Vascular

# The Oral Health Status of Patients with Peripheral Vascular Disorders: A Systematic Review



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## Abstract

**Objectives:** Periodontal disease and tooth loss were found to be associated with several peripheral vascular disorders (PVD). Nonetheless, an evaluation of the literature on the broader domains of oral health in individuals with PVD is lacking. This systematic review aims to collate the current evidence on the oral health status of individuals with PVD.

**Methods:** Five electronic databases were searched for studies assessing oral health parameters in individuals with PVD. Outcome measures considered were periodontal health, dentition status, caries indices, oral prostheses, oral pathologies and oral hygiene behaviours. The Newcastle-Ottawa scale was used to appraise the quality of the studies.

**Results:** From 3025 records identified, 24 studies involving 1232 participants with PVD were included in this review. In 9 studies, periodontitis was significantly more prevalent in PVD compared to non-PVD participants. A further 6 studies reported individuals with PVD also had significantly fewer teeth and increased rates of edentulism. Only 1 study reported a higher incidence of dental caries in PVD participants. Other aspects of oral health such as oral prosthesis, oral pathology and oral hygiene behaviours were seldom assessed.

**Conclusion:** The scarcity of studies reporting on broader domains limited our ability to arrive at a conclusion regarding the oral health status of individuals with PVD. Future studies ought to assess these domains in individuals with PVD and controls to gain a more complete understanding of oral health and its potential association with PVD.



## Keywords

Vascular medicine, peripheral vascular disease, oral health

## Introduction

Emerging evidence illustrates an association between certain oral health conditions, such as periodontal disease and tooth loss, and several peripheral vascular disorders (PVD).[1–6] The International Statistical Classification of Diseases and Related Health Problems (ICD) defines PVD as an umbrella term for any disorder affecting blood flow in arteries or veins outside the heart.[7] A recent meta-analysis[8] reported a significantly higher risk of periodontitis and tooth-loss amongst individuals with peripheral arterial disease (PAD), a type of PVD, than healthy controls. Their review only considered periodontitis and no other essential aspects of oral health as per the World Health Organisation's (WHO) manual for standardised oral health assessment. These include dentition status, dental erosions, oral mucosal lesions, dental caries, dentition and prosthesis status and oral hygiene behaviours.[9] More specifically, dental caries and poor oral hygiene had been investigated as markers of early initiation of atherosclerosis, and were found to be associated with increased carotid intima-media wall thickness.[10,11] Poor oral hygiene also increases the risk of periodontitis[12] and can lead to increased abundance of potentially pathogenic bacteria colonising the teeth.[13] These bacteria may exacerbate atherogenesis via the oral infection-inflammation pathway.[2]

Several measures have been taken by vascular surgeons regarding their patients' dental health, including dental antibiotic prophylaxis to prevent vascular graft infections following dental sepsis.[14,15] However, the oral health status of individuals with PVD remains incompletely assessed clinically. This is due to a lack of consensus regarding the need for oral health assessment in this group and whether this would warrant an improvement in outcomes of PVD. The aim of this study was to review the literature relating to the oral health status of individuals diagnosed with PVD. Further, where studies are available with controls (individuals without PVD), a comparison of the oral health status between these two groups was undertaken.

## Methods

### *Search strategy*

We used the Preferred Reporting Items for Systematic Review and Meta-analysis guidelines (see supplemental material for the checklist) for this systematic review. The Population Intervention/Exposure Comparator Outcome criteria were used to form the review question – What are the oral health findings (O) in individuals with PVD (P) whom have undergone oral health assessment (I) compared to individuals without PVD (C). Electronic database and hand searches for articles in April 2020 were conducted in the following databases: MEDLINE, SCOPUS, EMBASE, Web of Science and Cochrane Central Register of Controlled Trials. The search strategy was formed using the Medical Subject Headings and relevant free-text terms and was applied to each database (Supplementary Table 1).

### *Inclusion and Exclusion criteria:*

Inclusion criteria:

(i) Adults aged ≥ 18 years

(ii) Individuals with any vascular disease of arteries and veins outside the heart as grouped under the PVD diagnosis-related groups by the ICD[16]

(iii) Assessed any of the following oral health measures: dentition status, remaining/missing teeth, prevalence of dental disease including periodontal indices, dental caries indices, oral infections, oral pathology, presence/absence of oral prosthesis and oral hygiene behaviours

(iv) Published in English

Exclusion criteria:

(i) Systematic or literature reviews

(ii) Case reports

(iii) Studies with duplicate/overlapping cohorts.

***Data Extraction and quality assessment***

Study characteristics and data on participants' oral health were extracted from each included study and compiled on data extraction tables (Tables 1 and Supplementary 2 and 3). Titles and abstracts of all studies were independently screened by two reviewers (SAA and MM). Full texts of the selected studies were critically reviewed based on the inclusion and exclusion criteria. Although there were no disagreements, an arbitrator (GC) was available for mediation. For quality assessment, both reviewers independently used the Newcastle-Ottawa Scale (NOS) for case-control studies[17] and a modified form for cross-sectional studies (Supplementary Table 4).

**Results**

***Search results***

The search identified 3025 studies. RefWorks (*ProQuest Refworks, 2020*) was used to process the search results and to de-duplicate 80 studies. After application of inclusion and exclusion criteria, 58 studies were selected for full text screening, following which 24 studies comprising 1232 PVD participants were included in this systematic review (Figure 1).

***Characteristics of studies***

The characteristics of studies included in this systematic review are summarised in Table 1. These studies were published between 1994 and 2018 and were from 14 countries. 23 studies were on arterial disorders and one was on a venous disorder. 13 studies compared the oral health status between PVD participants and healthy controls[3,18–29], whilst three compared the oral health of PVD participants to controls with cardiac diseases.[30–32] Six studies[14,33–37] did not have controls. Another study included controls with cardiovascular disease; however, they did not measure oral health in the control group.[38] One study recruited edentulous PVD

participants as controls however no oral health assessment was conducted in this group, therefore a comparison was not done between cases and controls.[39]

***Examiner calibration and statistical power calculation***

Of the 24 studies, three studies reported examiner calibration through intraclass correlation coefficient[27], re-evaluation of random referred patients[29] and another through previously calibrated examiners using Kappa values (0.80 to 0.97).[35] Only one study provided details of statistical power calculation to determine sample size.[29]

***Case definition of PVD***

The case definition of PVD varied amongst the studies (see Table 1). Seven studies reported a PVD diagnosis of case groups but with no description of the parameters used to diagnose PVD.[31–35,38,39] One study used previous medical records of vascular disease.[36] Four studies used clinical findings of PVD as diagnostic parameters such as ankle-brachial index, clinical symptoms and Rose questionnaire.[14,26,27,29] Stansby et al.[14] reported the parameters used for diagnosing PAD but had only reported a diagnosis of aortic aneurysm (AA). Six studies used imaging parameters only such as angiography, computed tomography and Doppler ultrasonography.[3,19–21,23,28] Six studies used a combination of clinical findings and imaging parameters for diagnosis of PVD.[18,22,24,25,30,37]

### *Oral Health Measures*

#### *Periodontal health*

Periodontal health was assessed in 22 studies with results displayed in Supplementary Table 2. The case definition of periodontitis varied across each study (see Supplementary Table 2). Prevalence of periodontitis and moderate to severe periodontitis was reported to be significantly higher in participants with arteriosclerosis obliterans[25], Buerger's disease[22], PAD[18,26,27], carotid atherosclerosis[19], AA[20,21] and venous thromboembolic disease (VTED)[3] compared to non-PVD participants. Two studies found no differences between groups.[28,29] In studies with no controls, a high percentage of the PVD participants had periodontitis[23,24,37] except for one study.[33] Gingivitis was more prevalent in non-PVD than in PVD participants in four studies.[20,21,26,29]

Probing pocket depth (PPD) is a measurement of the distance from the gingival margin to the pocket base surrounding a tooth. This measurement is one of a range of clinical criteria used to diagnose and assess severity of periodontal diseases.[40] Aoyama et al.[30] and Çalapkorur et al.[29] found no difference between PVD and non-PVD participants in the mean PPD. Çalapkorur et al.[29] reported a significantly higher number of sites with PPD over 5mm amongst PVD participants. Likewise, a significantly higher number of sites with PPD over 4mm were seen in AA,[20,21,31,32] Buerger's disease,[22] carotid atherosclerosis[19] and PAD participants[18,27] compared to non-PVD participants. It is important to note that Çalapkorur et al.[29] defined periodontitis as having at least 5 teeth with at least 1 site of PPD equal to or greater than 5mm. This differed from the other studies which defined periodontitis as the presence of more than one site with PPD equal to or greater than 4mm in each quadrant.

Clinical attachment loss (CAL) indicates the extent of periodontal tissue support loss around a tooth. A significantly higher percentage of sites with CAL greater than 4mm was found amongst AA,[20,21] Buerger's disease[22], PAD[18,27] and VTED[3] participants compared to non-PVD participants. There was no significant difference in CAL greater than 4mm between PVD and non-PVD participants in two studies.[29,30]

Zaremba et al.[38] found four of 20 participants demonstrating presence of periodontal bacteria in their atherosclerotic plaques after carotid endarterectomy. These participants had significantly higher bleeding indices and PPD greater 4mm compared to participants with no periodontal bacteria in the atherosclerotic plaque. Mean CAL was not significantly higher in the group with periodontal bacteria present in atherosclerotic plaques than those without.

***Dentition status***

13 studies assessed the dentition status of PVD participants with results displayed in Supplementary Table 2.[3,14,18,20,23,28,30–36] Nine studies compared remaining or missing teeth in PVD to that of non-PVD participants.[3,18,20,28,30–32,34,36] All but three[28,31,34] reported significantly less retained teeth,[3,18,30,32] more missing teeth[20,30,36] or higher edentulism rates[30,36] in PVD compared to non-PVD participants. Three studies reported lower percentages of PVD participants who were edentulous.[14,23,33] Fernandes et al.[35] found that 96.1% of teeth were missing amongst 13 PVD participants.

***Dental Caries***

Five studies investigated caries in PVD participants with findings displayed in Supplementary Table 3.[27–29,33,35] The DMFT is the sum of the number of **D**ecayed, **M**issing and **F**illed **T**eeth due to dental caries in the permanent teeth. It is a widely used index to measure dental caries and dental treatment needs amongst populations.[9] Two studies reported the mean DMFT in PVD participants but had no controls.[33,35] Calapkorur et al.[29] reported no significant difference in the DMFT of PVD compared to non-PVD participants. Likewise, Friedlander et al.[28] found no significant difference in the mean number of carious retained roots or coronal/pulpal caries between PVD and non-PVD participants. Only one study reported a significantly higher DMFT index in PVD than non-PVD participants.[27]

***Other oral diseases***

Two studies commented on oral diseases other than caries and periodontal disease (see Supplementary Table 3).[28,33] Friedlander et al.[28] found no difference in the mean number of teeth with periapical lesions between PVD versus non-PVD participants. Immonen et al.[33] reported 80% of the PVD participants had an oral infection, with only 11% of them having "good oral health". Candida infection was present in 17% of dentate and 47% of edentulous PVD participants. 54% of dentate participants had intraosseous foci compared to 20% of edentulous participants. Periapical lesions and intraosseous foci are areas of localised chronic infection of dental origin that may influence chronic systemic diseases[41].

***Dental prosthesis***

Three studies assessed the presence of dental prosthesis in PVD participants (see Supplementary Table 3). Stansby et al.[14] reported 46% PVD participants had partial dentures. Another study reported that amongst a total of 56 dentures in 37 PVD participants,

45% of dentures were poor and had to be replaced[33]. A third study reported the mean number of implants but had no controls.[34]

***Oral hygiene behaviours***

Only one study investigated oral hygiene behaviours. They used a self-reported assessment of oral hygiene behaviours amongst AA participants[20]. Compared to the non-AA group, more AA participants had inaccurate brushing methods, less brushing time and frequency, no flossing and less routine dental examinations (Supplementary Table 3).

## Discussion

This review included broader oral health domains in the WHO's manual to assess oral health in individuals. Participants with PVD were found to have compromised oral health across various measures such as poorer periodontal health, more missing teeth and a higher prevalence of edentulism in comparison to non-PVD participants. However, the findings on dental caries and presence of periapical lesions in PVD and non-PVD participants were conflicting. Although not reported in the studies, reasons for this may include differences in dental health-seeking behaviour in PVD participants, and in the diagnostic protocols in different countries. Other aspects such as oral prosthesis, oral hygiene behaviours and oral pathology were seldom assessed.

This review has also considered other subtypes of PVD such as PAD, carotid atherosclerosis, AA, Buerger's disease and VTED. The assessment of oral health amongst individuals with a venous disorder was performed in only one of the included studies.[3] Association studies demonstrated a possible relationship with valvular incompetence in individuals with varicose veins,[42] the latter being a known risk factor for VTED.[43] This could be mediated by the role of certain bacteria in periodontal disease, which were found to be risk factors for vascular endothelial damage and pro-coagulation.[44,45] Despite Sanchez and colleagues'[3] significant oral health findings in their cohort with a venous disorder, further studies are required to confirm the validity of these findings and to compare the oral health status between individuals with venous and arterial disorders. Two studies in Yang and colleagues'[8] meta-analysis were excluded from our review as they assessed the risk of developing PVD in participants with prior periodontitis.[1,46]

***Tooth loss in PVD participants***

Several studies reported a significantly higher prevalence of tooth loss amongst PVD as opposed to non-PVD participants.[3,18,20,30,32,36] The putative mechanisms underpinning this finding could be varied. Firstly, tooth loss was shown to have a possible association with atherosclerosis, even with adjusting for shared risk factors including age, smoking, sex, diabetes mellitus and hypertension.[47] Secondly, an important mediator of incident tooth loss in PVD participants is antecedent periodontal disease. Periodontal infection via the oral infection-inflammation pathway, may promote systemic inflammation and exacerbate atherogenesis.[2] Tooth loss in turn may lead to compromised masticatory ability, causing an altered diet which may predispose to PVD.[48] Finally, the attitude and approach to dental disease management amongst participants and their dental care providers in different countries may have resulted in increased tooth loss.

***Dental prosthesis, other oral diseases and oral hygiene behaviours***

The studies reporting on the presence of dental prostheses in PVD participants were non-controlled and descriptive in nature.[14,33,36] Therefore, no inference could be made on this oral health domain in PVD and non-PVD participants. The current literature is also insufficient to establish any difference between PVD and non-PVD participants regarding oral diseases such as Candida infections, periapical lesions and intraosseous foci. For a more complete assessment of these domains, further analytical studies are required.

Poor oral hygiene behaviours have been associated with an increased risk of cardiovascular events and elevated concentrations of inflammatory molecules such as C reactive protein.[49] Conversely, improvements in oral hygiene have been shown to reduce the risk of cardiovascular events.[50] Although an important determinant of oral health, oral hygiene

behaviour was assessed in only one study.[20] That study only involved participants diagnosed with AA, who showed poor oral hygiene behaviours. Further analytical studies assessing oral hygiene behaviours in other PVD subsets are required.

***Overall appraisal of included studies and recommendations for future research***

Cross-sectional and case-control studies were the predominant study designs in this review. Twelve[14,19,21,23–25,33–35,37–39] studies did not adjust for shared risk factors that underpin both tooth loss and certain types of PVD such as age, diabetes mellitus, hypertension and smoking. Lack of adjustments in observational studies is a known limitation.

Key methodological limitations such as the lack of control groups[14,33–35,38], the use of controls with various cardiac[30–32] or vascular[24] co-morbidities, and unmatched controls have undermined the comparability of results between PVD and non-PVD participants. Furthermore, high heterogeneity of outcome measures and case definitions precluded a quantitative analysis. The case definitions of PVD and the clinical parameters employed for diagnosis were varied between the studies included. Several studies stated the diagnosis of PVD and its subtypes.[31–35,38,39] They did not, however, describe the parameters used to make the diagnosis. Some studies used imaging modalities to diagnose PVD.[3,20,21,23,28] These studies would have further benefited from categorising different PVD severities according to imaging findings. As this may allow correlation with associated oral health findings. This was evident in one study in which greater severities of periodontitis were seen with increased intima-media thicknesses on imaging.[19] Other studies utilised a combination of clinical and imaging tools to diagnose PVD which would also allow correlation of PVD severity with the oral health findings.[18,22,24,25,30,37] However, none of these studies had performed such correlation, which could have established whether or not increasing PVD severities are associated with poorer oral health findings.

Similarly, differences in case definitions of periodontitis, and value ranges for categorising different severities of periodontitis were observed. In addition, variations in the periodontal

indices used to assess clinical parameters of periodontal health were apparent. Such variations may cause inaccuracies in the prevalence of periodontitis amongst PVD participants. In general, studies would benefit from using a standardised case definition of periodontitis as recommended by Eke et al.[51] which is aimed for use in population-based research. Standardisation of clinical assessment parameters is also essential in future studies.[52]

Moreover, Bloemenkamp et al.[26] assessed periodontal disease using patient self-reporting. This method was shown to have acceptable validity for large-scale epidemiologic studies surveying periodontal disease.[53] Nevertheless, another review indicated that employing a combination of self-reporting alongside other clinical indicators, such as CAL and PPD, of periodontal disease may be most beneficial;[54] this approach was utilised in two studies.[20,21] Therefore, future studies utilising self-reporting methods amongst PVD participants may benefit by combining them with other parameters of assessing periodontal disease. One study performed periodontal examination one to two months postoperatively on PVD participants who had undergone vascular surgery.[34] There was no mention of whether these participants had received dental care during that period, when their oral health may have worsened.

The strengths of this review relate to the assessing a spectrum of essential oral health domains, other than periodontitis, in participants with various subtypes of PVD as per WHO guidance. The principle limitation was the inability to undertake a quantitative analysis due to high heterogeneity of the included studies. Additionally, only four of the 24 studies were considered of high quality (scores greater than six) according to the NOS scale. Further, only three of the 16 studies that included controls were graded as high quality. Therefore, the scarcity of high quality studies compromises the ability to establish a clear description of the oral health status amongst PVD participants. Nor does it permit a meaningful comparison to be made between PVD and non-PVD participants. Several recommendations for future

research on this topic are listed in Table 2 based on the format recommended by Brown et al.[55] These recommendations include but are not limited to:

- Future studies to assess the magnitude of the relationship between PVD and oral health parameters other than periodontal disease and tooth loss
- Using standardised case definitions for PVD and periodontitis
- Using standardised parameters for PVD diagnosis and oral health assessment according to WHO guidance and customised from Oral Health Assessment and Review Dental Clinical Guidance of the Scottish Dental Clinical Effectiveness Programme.[56]
- Assessing the effect of oral health treatment on PVD.

## Conclusion

Due to the paucity of the high quality studies addressing oral health domains other than periodontal disease and tooth loss, a definitive conclusion regarding oral health status/conditions in individuals with PVD could not be made. Therefore, it is not yet possible to make an evidence-based recommendation regarding the value of routine oral health assessment in individuals with PVD. However, on considering the evidence regarding the link between oral and systemic health, it would be good practice to advise on oral health assessment and maintenance in individuals with PVD.

## Conflicts of interest

The Authors declare that there is no conflict of interest.

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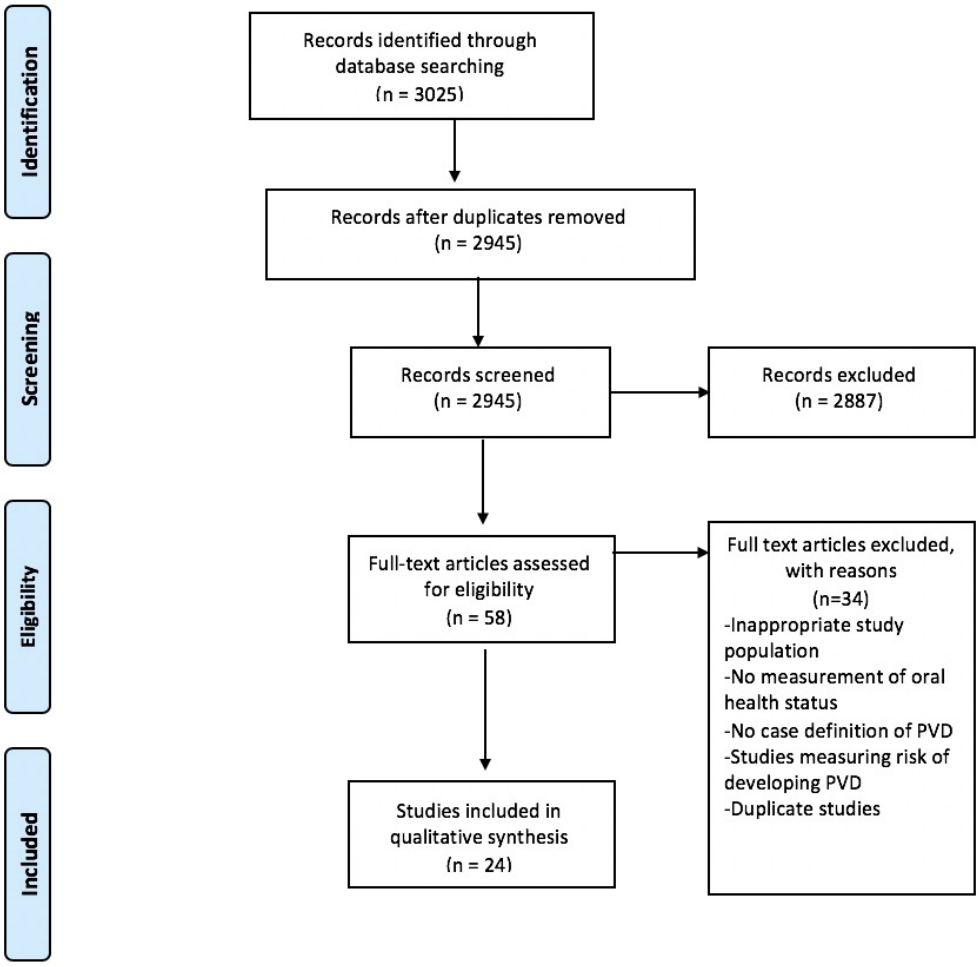


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of literature search and paper selection process.

149x149mm (144 x 144 DPI)

**Table 1** Characteristics of included studies

| Author, country, year | Study design | N, Mean Age (± SD), M/F | | Examiner calibration/ Statistical power calculation | Clinical Parameters of PVD/PVD diagnosis |
|---|---|---|---|---|---|
| | | PVD group | Non-PVD group | | |
| Stansby et al., 1994, England | CSS | 70, 68, 32/18 | N/A | N/A | ABI ≤ 0.90/ PAD or AA |
| Hamasha et al., 1998, USA | CSS | 19, 80.7, unspecified | N/A | N/A | Medical record of atherosclerotic vascular disease |
| Häyrinen-Immonen et al., 2000, Finland | Prospective clinical study | 50, 65, 33/17 | N/A | N/A | AAA |
| Bloemenkamp et al., 2002, Holland | CSS | 212, 48.2 ± 7.0, 0/212 | 475, 45.5 ± 3.1, 0/475 | N/A | Clinical symptoms (Intermittent claudication, non-healing ulcers, gangrene); angiographic findings indicating ≥50% of stenosis in peripheral arteries/ PAD |
| Cairo et al., 2004, Italy | Controlled clinical and laboratory trial | 19, 71.37 ±6.14, 14/5 | 21, 73.33 ± 6.11, 15/6 | N/A | Carotid stenosis |
| Kurihara et al., 2004, Japan | CCS | 32, 73, 27/5 | Unspecified | N/A | Angiographic, ultrasonic and CT evaluation of AAA |
| Iwai et al., 2005, Japan | CCS | 14, 60, 14/0 | 7, unspecified, 5/2 | N/A | Shionoya's Criteria; angiographic findings; Allen's test/ Buerger's disease |
| Chen et al., 2007, Japan | CCS | 19, 56.6 ± 11, 19/0 | 19, 56.6 ± 11, 19/0 | N/A | Shionoya's Criteria; angiographic findings; Allen's test/ Buerger's disease |
| Chen et al., 2008, Japan | CCS | 25, 67.6 ± 10, 21/4 | 32, 63.10 ± 10, 28/4 | N/A | Clinical symptoms, angiographic findings and ABI/ PAD |

**Table 1 (Continued)**

| | | | | | |
|---|---|---|---|---|---|
| Friedlander et al., 2010, USA | CCS | 36, 64.4 ± 10.0, 97.2%/2.8% | 36, 64.9 ± 10. 10, 97.2%/2.8% | N/A | Carotid stenosis confirmed by Doppler ultrasonography |
| Toyofuku et al., 2011, Japan | CCS | 53, 69.0 ± 9.1, 49/4 | 21, 70.6 ± 8.9, 20/1 | N/A | Fontaine Classification, angiographic, ultrasonic and CT imaging/ Arteriosclerosis obliterans |
| Zaremba et al., 2012, Poland | CCS | 20, 67, 13/7 | unspecified | N/A | Internal carotid artery stenosis |
| Sánchez et al., 2013, Spain | CCS | 97, 60.63± 15.07, 43/54 | 100, 61.86 ± 8.49, 54/46 | N/A | Doppler ultrasonography and CT angiography/VTED |
| Soto-Barreras et al., 2013, Mexico | CCS | 30, 63.23 ± 9.06, 27%/73% | 30, 61.86 ± 8.49, 30%/70% | Yes/N/A | ABI ≤ 0.90. <ild-to-moderate: 0.40 to 0.90<br>Severe: <0.4/ PAD |
| Figuero et al., 2014, Sweden | CSS | 42, 68.95 ± 8.65, 31/11 | N/A | N/A | Carotid stenosis, PAD and AAA |
| Fernandes et al., 2014, Brazil | CSS | 13, 68.5 ± 10.1, 6/7 | N/A | Yes/N/A | AA and carotid stenosis |
| Suzuki et al., 2014, Japan | CCS | 12, 70.6 ± 3.5, 9/3 | 25, 71.4 ± 2.1, 60%/40% | N/A | AAA |
| Ding et al., 2014, China | CCS | 89, 57.8±7.6, 79/10 | 59, 56.8±6.3, 44/15 | N/A | AA diagnosed by CT showing aortic diameter >50% than normal |
| Suzuki et al., 2015, Japan | CCS | 25, 71.4 ± 2.1, 60%/40% | 142, 68.8 ± 0.4, 78.2%/ 21.8% | N/A | AAA |
| Igari etl al., 2015, Japan | CSS | 58, 48, 55/3 | N/A | N/A | Buerger's disease diagnosed by Shionoya's criteria |
| Çalapkorur et al., 2016, Turkey | CSS | 40, 60.45 ± 9.94, 32/8 | 20, 60.4 ± 9, 18/2 | N/A/Yes | ABI ≤ 0.90 and Rose questionnaire/ PAD |
| Aoyama et al., 2017, Japan | CSS | 34, 65.6 ± 11.8, 23/11 | 956, 64.4 ± 13, 693/263 | N/A | Clinical symptoms, ABI and angiographic findings/PAD |

**Table 1 (Continued)**

| | | | | | |
|---|---|---|---|---|---|
| Nicolaiciuc et al., Romania, 2018 | CCS | N =35<br>IMT > 1mm: 18<br>Atheroma plaque: 17,<br>IMT > 1mm: 62.9 (±10,2)<br>Atheroma plaque: 62.5(±10/8),<br>IMT > 1mm: 9/9<br>Atheroma plaque: 12/5 | 15, 40,8 (±10,9), 4/11 | N/A | Evaluation done with USS to measure IMT and record presence of atherosclerotic plaques/Carotid atherosclerosis |
| Ding et al., China, 2018 | CCS | 169, 56.2, 30/39 | 156, 54.8 ± 5.0, 129/27 | N/A | AA diagnosed by CT when aortic diameter >50% normal diameter |

*AA, Aortic aneurysm; AAA, Abdominal aortic aneurysm ;ABI, ankle brachial index; CCS, case-control study; CSS, cross-sectional study; CT, Computed tomography; F, Female IMT, intima-media thickness; M, male; PAD, peripheral artery disease; PVD, peripheral vascular disease; SD, Standard deviation; USS, ultrasound scan; VTED, Venous thromboembolic disease.*

**Table 2** Research recommendations (based on format from Brown *et al*., 2006)[55]

| Core elements | Recommendation for future research |
|---|---|
| (E) Evidence (Current) | Systematic review identified predominantly cross-sectional and case-control studies |
| | Future studies should focus on assessing the magnitude of the relationship between poor oral health findings and PVD |
| (P) Population | Adults with PVD aged ≥ 18 years old |
| | Standardised clinical parameters for diagnosis of any subset of PVD |
| (I)Intervention/exposure | Standardised periodontal probing and mouth examination protocol |
| | Assessment of oral health parameters as per the WHO's manual for standardised oral health assessment using Oral Health Assessment and Review Dental Clinical Guidance of the Scottish Dental Clinical Effectiveness Programme[56] |
| | Assessment of dental caries indices, oral pathologies, oral hygiene behaviours |
| (C) Comparison | Adults aged ≥ 18 years old without PVD |
| (O) Outcomes | Periodontal disease prevalence according to Eke et al.[51] definition of periodontitis |
| | Dentition status and presence of dental prosthesis in individuals with PVD |
| | Prevalence of dental caries and oral pathologies |
| | Oral hygiene behaviours in individuals with PVD |

**Supplementary Table 1** Population intervention/exposure comparator outcome – Search terms

| PICO | Search terms |
|---|---|
| Population | Abdominal aortic aneurysm, aortic aneurysm, aneurysm, aorta, arterial occlusive diseases, atherosclerosis, atherosclerotic plaque, carotid artery diseases, carotid stenosis, intermittent claudication, peripheral arterial disease, peripheral vascular diseases, thrombosis, upper extremity deep vein thrombosis, vascular diseases, venous thrombosis |
| Intervention/Exposure | Oral health, dental care |
| Outcome | Alveolar bone loss, aggressive periodontitis, chronic periodontitis, dentition, dental attendance, dental caries, dental prosthesis, flossing, furcation defects, gingivitis, gingival diseases, mouth, mouth diseases, oral hygiene, oral pathology, periodontal diseases, periodontitis, periapical periodontitis, periapical granuloma, toothbrushing, tooth mobility, tooth loss |

**Supplementary Table 2** Case definitions, periodontal health and dentition status findings

| Author | Periodontal indices<br>Periodontitis case definition | Dentition status | Periodontal results |
|---|---|---|---|
| Stansby et al., 1994 | CPITN<br>Unspecified case definition | 37% of PVD participants were edentate<br>Dentate PVD participants had a mean number of 16.33 ± 9.10 teeth | 0 participants with healthy tissue (CPITN 0)<br>4 participants with no significant pathology (CPITN 1-2)<br>12 participants with moderate pathology (CPITN 3)<br>28 participants with significant pathology (CPITN 4) |
| Hamasha et al.,1998 | N/A | PVD participants had significantly more missing teeth than controls (22.1 vs 19.5, p=0.01)<br>Edentulism was significantly higher in PVD participants compared to controls (57.9% vs 32.0 %, respectively, p=0.02) | N/A |
| Häyrinen-Immonen et al., 2000 | Periodontitis diagnosis<br>CPI<br>PPD ≥3.5mm | 30% of PVD participants were edentate<br>Mean number of teeth of PVD participants was 9.3 | 17% of AAA participants teeth has severe periodontitis.<br>93% of AAA participants had poor periodontal status (CPI scores>3). |
| Bloemenkamp et al., 2002 | Self-reported periodontitis<br>Self-reported gingivitis<br>Unspecified definition | N/A | % of PAD participants with self-reported periodontitis was significantly higher than controls (31 (23%) vs 33 (8%) 3.0 (1.4–6.3) (multi-adjusted OR 95% CI))<br>% of PAD participants with self-reported gingivitis was significantly less than controls (31 (23%) vs 67 (17%) 1.2 (0.6–2.2) (multi-adjusted OR (95%CI)) |
| Cairo et al., 2004 | BOP, CAL, PI, PPD<br>(Mean ±SD)<br>Unspecified definition | Mean tooth loss = 13.0 ± 6.25 | Mean BOP in CS participants: 58.85 ± 27.15%<br>Mean CAL in CS participants: 4.69 ± 1.58mm<br>Mean PI in CS participants: 75.95 ± 26.81%<br>Mean PPD in CS participants: 2.87 ± 0.82mm |
| Kurihara et al., 2004 | PPD<br>Normal periodontal health: PPD < 2mm<br>Moderate periodontitis: PPD 2-5mm<br>Severe periodontitis: PPD≥5mm | 15% of PVD participants were edentate | No AAA participants were considered to be periodontally healthy<br>22% of AAA participants had mild periodontitis<br>63% of AAA participants had severe periodontitis |

**Supplementary Table 2** (Continued)

| | | | |
|---|---|---|---|
| Iwai et al., 2005 | PPD<br>Normal periodontal health (Grade A) : PPD < 2mm<br>Moderate periodontitis (Grade B) : PPD 2-5mm<br>Severe periodontitis (Grade C): PPD≥5mm<br>Grade D: Edentulous | N/A | 0 participants in group A<br>4 participants in group B<br>9 participants in group C<br>1 participant in group D |
| Chen et al., 2007 | CAL, PPD<br>Mild periodontitis: less than 10% of site with CAL ≥4mm,<br>Moderate-severe periodontitis: >10% sites with CAL ≥4mm | No significant difference in number of residual teeth between BD participants and controls (20.2 vs 25.7, respectively p = 0.067 | Periodontitis was significantly more prevalent in BD participants than controls (89.5% vs 26.7%, p <0.001).<br>Moderate- severe periodontitis was significantly more prevalent in BD participants than controls (68.8% vs 13.1%, p<0.001).<br>No statistically significant difference in prevalence of mild periodontitis between BD participants and controls (21.1% vs 13.3%, p=1)<br>PD and CAL □4mm was significantly higher in BD participants (14.3% and 22.6%, respectively) than controls (2.2% and 5.1%, respectively) p = 0.016 and p<0.001, respectively |
| Chen et al, 2008 | CAL, PPD<br>Presence of ≥ 1 site with PPD or CAL ≥4mm in each quadrant | PVD participants had significantly less residual teeth than controls (13.2 vs 24.5, respectively, p<0.001) | Significantly more PAD participants were diagnosed with periodontitis compared to controls ( 68.0% vs 31.0% p = 0.004)<br>PAD participants had a significantly higher percentage of sites with CAL >4mm compared to controls (39.0% vs 13.4% respectively, p=0.007)<br>PAD participants had a significantly higher percentage of sites with PPD >4mm compared to controls (14.8% vs 2.6% respectively, p=0.003) |
| Friedlander et al., 2010 | MPI, presence of furcal lesions, presence of pericoronitis<br>Unspecified definition | Number of missing teeth in CS participants was not significantly higher than controls (8.5 ± 6.3 vs. 7.1 ± 6.8 respectively, p=0.390) | No significant difference between the mean number of furcal lesions between CS participants and controls (1.3 ± 1.5 vs 0.8 ± 1.1 respectively, p=0.153)<br>No significant difference between the mean number of sites with pericoronitis between CS participants and controls (0.03 ± 1.7 vs 0.1 ± 0.7 respectively, p=0.475)<br>CS participants had a significantly higher MPI than controls (15.5 ±10.4 vs 7.9 ± 8.1 respectively, p =0.001) |
| Toyofuku et al., 2011 | CAL<br>Periodontally healthy= PPD <4mm<br>Moderate periodontitis= PPD 4-6mm<br>Severe periodontitis PPD = ≥7mm | N/A | 96% of ASO participants and 100% of controls had periodontitis<br>Moderate periodontitis was higher in controls than ASO participants (52% vs. 32% respectively)<br>Severe periodontitis was higher in PVD participants than controls (44% vs. 38%) |

**Supplementary Table 2** (Continued)

| | | | |
|---|---|---|---|
| Zaremba et al., 2012 | BOP, CAL. PI, PPD<br>Unspecified definition | N/A | Mean bleeding index was significantly higher in CS participants with bacteria in atheromatous plaque than those without (50% vs. 24%)<br>% of pockets ≥4mm was significantly higher in CS participants with bacteria in atheromatous plaque than those without (22.8% vs 5.1%)<br>No significant in difference in CAL between CS participants with bacteria in atheromatous plaque than those without (3.88mm vs 3.51) |
| Sánchez et al., 2013 | BOP, CAL, CPITN, GI, PPD, Simplified oral hygiene index (OHI-S)<br>Unspecified definition | Number of teeth in VTED participants was significantly less than controls ( 21.61+/-7.77 vs. 26.80+/-2.19 respectively p<0.001) | Significantly more VTED participants were diagnosed with periodontitis than controls 71(73.19%) vs 45(45%) respectively, p<0.001).<br>BOP was significantly higher in VTED participants versus controls (45.86 ± 35.07 vs 21.77 ± 11.33, respectively, p<0.001)<br>Mean CAL was statistically higher in VTED participants versus controls (3.84 ± 1.54 vs 1.41 ± 0.62 respectively, p<0.001)<br>Mean CAL was statistically higher in VTED participants versus controls (3.84 ± 1.54 vs 1.41 ± 0.62 respectively, p<0.001)<br>GI was significantly higher in VTED participants versus controls (1.56 ± 0.95 vs 21.77 ± 1.00 ± 0.71, respectively, p<0.001)<br>OHI-S scores was significantly higher in VTED participants versus controls (1.19 ± 0.78 vs 0.17 ± 0.37, p<0.001) indicating poorer oral hygiene<br>Mean PPD was statistically higher in VTED participants versus controls (3.02 ± 1.27 vs 2.51 ± 0.89 respectively, p= 0.001) |
| Soto-Barreras et al, 2013 | CAL<br>CAL ≥ 4mm in 30% of measured sites | N/A | More PAD participants were diagnosed with periodontitis compared to controls (90% vs 56%)<br>Presence of PD and AL □4mm was significantly higher in PAD group than controls (16.3% and 45.1%, respectively) vs. (9.3% and 27.4%, respectively) p = 0.0272<br>PAD showed a positive association with periodontitis ( OR = 8.18; 95% CI = 1.21 to 35.23; p = 0.031) |
| Fernandes et al, 2014 | Healthy Sextants, Bleeding Sextants, Presence of Calculus, PPD<br>Unspecified definition | Out of 13 PVD participants, 400 (96.1%) teeth were missing | No healthy sextants were detected in PVD participants<br>No bleeding sextants were detected in PVD participants<br>1.3% of sextants had calculus<br>1.3% of sextants had PPD 4-5mm.<br>No sextants had PPD> 6mm |
| Figuero et al, 2014 | BOP, Furcation, Mobility, Plaque scores, PPD | No significant difference between the number of residual teeth of PVD participants | Mean BOP was 63.11% ± 22.85%.<br>Mean number of teeth with furcation involvement was 2.68 ± 2.20 |

**Supplementary Table 2** (Continued)

| | | | |
|---|---|---|---|
| | Unspecified definition | vs controls (20.2 vs 25.7 respectively, p=0.067) | Mean number of mobile teeth was 0.68 ± 1.47<br>45% of PVD participants had a periodontitis diagnosis<br>Mean plaque scores in PVD participants were 68.74% ± 22.85%<br>Mean number of pockets of 4mm was 13.92 ± 7.82<br>Mean number of pockets of 5-6mm was 8.39 ± 8.42.<br>Mean number of pockets >7mm was 1.89 ± 3.79<br>Mean number of suppurating pockets was 3.58 ± 8.45 |
| Suzuki et al, 2014 | BOP, CPI, PPD<br>Unspecified definition | Number remaining teeth statistically comparable between AAA participants and controls (16.8 ± 2.8 vs 19.8 ± 1.6 respectively) | BOP was Statistically comparable between AAA participants and controls<br>CPI was Statistically comparable between AAA participants and controls<br>AAA participants had significantly higher PPD than controls (3.01 ± 0.26mm vs2.52 ± 0.05 mm respectively, p<0.05) |
| Ding et al, 2014 | BOP, BI, CAL, PD, PLI<br>Mild: CAL 1-2mm<br>Moderate periodontitis: CAL 3-4mm<br>Severe peridontitis: CAL >5mm | N/A | Gingivitis was significantly higher in controls than in AA participants (18 vs 5, respectively p<0.01)<br>Mild periodontitis was significantly higher in controls than AA participants (25 vs 15,l respectively p<0.01)<br>Moderate (36 vs 4, p<0.01) and severe periodontitis (33 vs 5, p<0.01) was significantly higher in AA participants than controls<br>BI , CAL, PD, PLI were all significantly higher in AA participants than controls<br>BI (3.4 ± 0.5 vs 2.1 ± 0.7 respectively, p<0.01)<br>CAL (4.7 ±0 .8 vs 3.0 ± 0.7 respectively, p<0.01)<br>PLI (\|2.4 ± 0.6 vs 2.0 ± 0.6 respectively, p<0.01)<br>PD (5.2 ± 0.8 vs 4.3 ± 0.7 respectively, p<0.01 |
| Igari et al, 2015 | PD<br>Normal (Grade A) : PD < 2mm<br>Moderate periodontitis (Grade B) : PD 2-5mm<br>Severe periodontitis (Grade C): PD > 5mm<br>Grade D: Edentulous | N/A | Consent was only sought from 19 of the 58 BD participants<br>Grade A: 1 BD participant<br>Grade B: 7 BD participants<br>Grade C: 9 BD participants<br>Grade D: 2 BD participants<br>More than half of the BD participants (11 out of 19) had severe periodontitis |
| Suzuki et al, 2015 | BOP, CPI, PPD<br>Unspecified definition | PVD participants had significantly less residual teeth than controls (14.6 ± 2.0 vs 20.9 ± 0.7 respectively, p<0.05) | BOP was statistically comparable between AAA participants and controls<br>CPI was statistically comparable between AAA participants and controls<br>AAA participants have significantly higher PPD than controls (3.01 ± 0.26mm vs 2.52 ± 0.05 mm respectively, p<0.05) |

**Supplementary Table 2** (Continued)

| | | | |
|---|---|---|---|
| Çalapkorur et al, 2016 | BOP, CAL, GI, Gingivitis diagnosis, PI, PPD<br>Chronic periodontitis defined as the presence of at least 5 teeth with ≥1 site of PPD ≥5mm, CAL ≥2mm, BOP and 30% radiographic bone loss. | N/A | No significant difference between BOP of PAD participants and controls (5.18 vs 3.41 respectively, p = 0.058)<br>No significant difference between mean CAL of PAD participants and controls (3.88 ± 0.91 vs 3.82 ± 0.69 respectively, p = 0.642)<br>No significant difference between median plaque indices of PAD participants and controls (2.00 vs 1.91 respectively, p = 0.456)<br>No significant difference between median PPD of PAD participants and controls (2.5 vs 2.1 respectively, p = 0.072)<br>No significant difference between PAD participants and controls in localised (21% vs 5% respectively) and generalised (9% vs 3% respectively) chronic periodontitis |
| Aoyama et al, 2017 | BOP, CAL, PPD<br>Unspecified definition | Edentulism was significantly higher in PVD participants compared to controls (18% vs 5%, respectively, p=0.0139)<br>PVD participants had significantly more missing teeth than controls (17.5 ± 11 vs 10.9 ± 8.7, respectively, p <0.0001) | Mean PPD was not significantly different between PAD participants and controls (2.28 ± 0.4mm vs 2.42 ± 0.58mm respectively, p= 0.2021)<br>Mean CAL was not significantly different between PAD participants and controls (2.90 ± 0.88mm vs 3.10 ± 1.07mm respectively, p= 0.5979) |

**Supplementary Table 2** (Continued)

| | | | |
|---|---|---|---|
| Nicolaciuc et al, 2018 | BOP, CAL, PD, PI<br>Mild periodontitis: CAL between 1-2 mm<br>Moderate periodontitis: CAL between 3-4 mm<br>Severe periodontitis: CAL > 5mm | N/A | • Mean BOP was not significantly different between PVD participants and controls (16.00 ± 18.80% vs 16.20 ± 20.20% respectively, p= 0.9569)<br>• Mean BOP was significantly higher in IMT > 1mm and atheroma group vs controls (43.4 ± 32.1 and 31.6 ± 23.4, respectively vs 35.7 ± 24.6)<br>• Participants with PD > 4mm was significantly higher in IMT > 1mm and atheroma group than controls (6 and 12, respectively vs 4, p=0.022)<br>• Mean number of sites with PD > 4mm was significantly higher in IMT > 1mm and atheroma group vs controls ( 33.8 ± 32.3 and 51.1 ± 31.1, respectively vs 35.4 ± 51.3, p = 0.040)<br>• Participants with superficial periodontitis was significantly higher in controls than IMT > 1mm and atheroma group (8 vs 4 and 2, respectively)<br>• Participants with moderate periodontitis was significantly higher in IMT > 1mm group and atheroma group than controls (8 and 3, respectively vs 5)<br>• Mean number of sites with PD > 4mm was significantly higher in IMT > 1mm and atheroma group vs controls ( 33.8 ± 32.3 and 51.1 ± 31.1, respectively vs 35.4 ± 51.3, p = 0.040<br>• Participants with superficial periodontitis was significantly higher in controls than IMT > 1mm and atheroma group (8 vs 4 and 2, respectively)<br>• Participants with moderate periodontitis was significantly higher in IMT > 1mm group and atheroma group than controls (8 and 3, respectively vs 5)<br>• Participants with moderate periodontitis was significantly higher in IMT > 1mm group and atheroma group than controls (8 and 3, respectively vs 5)<br>• Participants with severe periodontitis was significantly higher in IMT > 1mm and atheroma groups than controls ( 6 and 12, respectively vs 2, p = 0.006) |
| Ding et al, 2018 | BOP, CAL, PD, PI<br>Classification of Periodontal | Missing teeth was significantly higher in AA participants than controls (1.7 vs 0.5 | Gingivitis prevalence was significantly higher in controls compared to AA participants (54 (34.6% vs 21 (12.4%) respectively, p = 0.000) |

**Supplementary Table 2** (Continued)

| | | | |
|---|---|---|---|
| | Diseases and Conditions used to diagnose chronic periodontitis | respectively, p = 0.000) | Periodontitis prevalence was significantly higher AA participants than controls ( 148 (87.6%) vs 87 (55.8%) respectively, p = 0.000)<br>Mild periodontitis was significantly higher in controls compared to AA participants ( 31 (18.3%) vs 62 (39.7\|%) respectively, p = 0.000)<br>Moderate periodontitis was significantly higher in AA participants compared to controls (89 (52.7%) vs 15 (9.6%) respectively, p = 0.000)<br>Severe periodontitis was significantly higher in AA participants than controls (28 (16.6%) vs 10 (6.4%), p = 0.000)<br>BI was significantly higher in AA participants than controls (3.0 ± 0.5 vs 2.1 ± 0.7 respectively, p = 0.000)<br>CAL was significantly higher in AA participants than controls (3.09 ± 1.27 vs 2.25 ± 1.03 respectively, p = 0.000)<br>PD was significantly higher in AA participants than controls (3.55 ± 0.52 vs 2.29 ± 0.49 respectively, p = 0.000)<br>PI was significantly higher in AA participants than controls (2.4 ± 0.6 vs 2.0 ± 0.4 respectively, p = 0.000 |

*AA: Aortic aneurysm; BD: Buerger's disease; BOP: bleeding on probing; CAL; clinical attachment loss; CI: Confidence interval; CPI: Community Periodontal Index; CPITN: Community Periodontal Index of Treatment Needs; CS: Carotid stenosis DMFT: decayed, missing, filled teeth; GI: Gingival index; IMT: Intima-media thickness; MPI: Mattila Pantomography Index; OHI-S: simplified oral hygiene index; OR: Odds ratio; PI: plaque index; PPD; pocket probing depth; PVD: peripheral vascular disease; SD: Standard deviation; VTED: Venous thromboembolic disease*

**Supplementary Table 3** Dental caries, oral pathology, oral infection, oral hygiene behaviours, oral prosthesis indices and findings

| Author | Dental caries (Indices used and findings) | Oral pathology (Indices used and findings) | Oral hygiene behaviours (Indices used and findings) | Oral prosthesis (Indices used and findings) |
|---|---|---|---|---|
| Stansby et al, 1994 | N/A | N/A | N/A | • Presence of dentures<br>32 (46%) of PVD participants had partial dentures |
| Häyrinen-Immonen et al, 2000 | • DMFT<br>• Number of teeth with deep caries<br>Overall mean DMFT of AAA participants: 26 ± 4.8<br>1 participant had deep caries, and this tooth had to be extracted for this reason<br>19 (54%) of dentate AAA participants had interosseous foci<br>3 (20%) of edentate AAA participants had interosseous foci | • Interosseous foci<br>• Presence of Candida infection<br>41 (80%) AAA participants had oral infection.<br>13 AAA participants (26%) suffered from oral Candida infection. | N/A | • Number of dentures<br>37 participants had a total of 56 dentures with 45% of them being too old, unfit or broken |
| Friedlander et al, 2010 | • Caries index<br>Mean number of teeth with coronal/pulpal caries was statistically comparable between CS participants and controls (2.4 ± 3.5 vs 2.1 ± 2.5, respectively, p=0.689 | • Number of retained roots with carious lesions<br>• Number of teeth with periapical lesions<br>Mean number of carious retained roots was not significantly different between CS participants and controls (1.4 ± 1.6 vs 0.8 ± 1.6, respectively, p=100). Mean number of teeth with periapical lesions between CS participants and controls was not statistically significant (1.5± 2.4 vs 0.8 ± 1.5 respectively, p=0.109) | N/A | N/A |

**Supplementary Table 3** (Continued)

| | | | | |
|---|---|---|---|---|
| Soto-Barreras et al, 2013 | • DMFT<br>Participants with PAD had a significantly higher DMFT index than controls (21.4 +/- 2.6 vs 18.3 +/- 3.4, p<0.0002) | N/A | N/A | N/A |
| Fernandes et al, 2014 | • DMFT<br>Mean DMFT of PVD participants was 31.5 ± 1.4 | N/A | N/A | N/A |
| Figuero et al, 2014 | N/A | N/A | N/A | • Number of implants<br>Mean number of implants: 0.45 +/-1.47 |
| Çalapkorur et al, 2016 | • DMFT<br>Mean DMFT of PAD participants was statistically comparable to controls (14.60 ± 5.46 vs 12.65 ±6.30, p= 0.221) | N/A | N/A | N/A |
| Ding et al, 2018 | N/A | N/A | • Brushing method: Horizontal brushing was significantly higher in AA participants than controls (63 vs 16 respectively, p = 0.000). Vertical brushing was significantly higher in Controls than AA participants (96 vs 44 respectively, p = 0.000). Mixed brushing was not significantly different between AA participants and controls (62 vs 44 respectively, p = 0.000)<br>• Frequency, time and sites: Brushing < 1 time/day was significantly higher in AA participants than controls (82 vs 47 respectively) whereas brushing ≥ 1 time/day was significantly higher in controls than participants (87 vs 109 respectively p = 0.001). Brushing time | N/A |

**Supplementary Table 3** (Continued)

| | | | |
|---|---|---|---|
| | | | <1minute was significantly higher in AA participants than controls (95 vs 52 respectively) whereas >3minute was significantly higher in controls than AA participants (34 vs 16 respectively, p = 0.002). Brushing every surface was significantly more in controls than AA participants (92 vs 76 respectively, p = 0.012)<br>• Average lifespan of toothbrush: Lifespan of a tooth brush more than three months was seen significantly more in AA participants than controls (139 vs 102 respectively, p = 0.001)<br>• Flossing: Absence of flossing was significantly higher in AA participants than controls (163 vs 141 respectively, p = 0.012)<br>• Supragingival scaling: Supragingival scaling <once/year was significantly higher in AA participants than controls (160 vs 128 respectively, p = 0.000)<br>• Dental appointments: Absence of periodic dental examination was significantly higher in AA participants than controls (154 vs 124 respectively, 0.003) |

*AA: Aortic aneurysm; CS: Carotid stenosis; DMFT: Decayed, missing, filled teeth; PAD: Peripheral arterial disease; PVD: Peripheral vascular disease.*

**Supplementary Table 4** Quality assessment of the included studies using the Newcastle Ottawa Scale ($N = 24$)

| Author, year | Selection[a] | Comparability[b] | Outcome[c] | Score |
|---|---|---|---|---|
| Stansby et al.,1994[14] | *** | 0 | * | 4 |
| Hamasha et al., 1998[36] | *** | ** | ** | 7 |
| Hayrinen-Immonen et al., 2000[33] | * | 0 | * | 2 |
| Bloemenkamp et al., 2002[26] | ** | ** | * | 5 |
| Cairo et al., 2004[39] | ** | 0 | 0 | 2 |
| Kurihara et al., 2004[23] | * | 0 | 0 | 1 |
| Iwai et al., 2005[24] | ** | 0 | 0 | 2 |
| Chen et al., 2007[22] | ** | ** | ** | 6 |
| Chen et al., 2008[18] | *** | ** | ** | 7 |
| Friedlander et al. 2010[28] | ** | ** | ** | 6 |
| Toyofuku et al., 2011[25] | *** | 0 | * | 4 |
| Zaremba et al., 2012[38] | * | 0 | * | 2 |
| Sánchez et al., 2013[3] | *** | * | ** | 5 |
| Soto-Barreras et al., 2013[27] | *** | ** | * | 6 |
| Figuero et al., 2014[34] | *** | 0 | 0 | 3 |
| Fernandes et al., 2014[35] | * | 0 | * | 2 |
| Suzuki et al., 2014[31] | * | * | ** | 4 |
| Ding et al., 2014 | *** | * | ** | 6 |
| Suzuki et al., 2015[32] | * | 0 | * | 2 |
| Igari et al., 2015 | *** | 0 | * | 4 |
| Çalapkorur et al., 2014[29] | *** | ** | ** | 7 |
| Aoyama et al., 2017[30] | ** | ** | ** | 6 |
| Nicolaiciuc et al., 2018[19] | *** | 0 | ** | 5 |
| Ding et al., 2018[20] | **** | ** | ** | 8 |

[a] A maximum of five stars can be awarded for selection

[b] A maximum of two stars can be awarded for comparability

[c] A maximum of three stars can be awarded for outcome

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | Not applicable |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 4<br>Supplemental table 1 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5<br>Supplemental table 1 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 5 |

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | Not applicable |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 5 |



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 5 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | Not applicable |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 5<br>Figure 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 5,6<br>Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 5 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 7,8,9,10<br>Table 2 and 3 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Not applicable |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 5 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Not applicable |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 11, 12, 13 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 14,15,16 |

# PRISMA 2009 Checklist

| | | | |
|---|---|---|---|
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 17<br>Table 4 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 17 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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