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The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease

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Dietrich T, Sharma P, Walter C, Weston P, Beck J. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease.

Abstract

Objectives: The objective of this study was to systematically review the epidemiological evidence for an association between periodontitis (PD) and incident atherosclerotic cardiovascular disease (ACVD), including coronary heart disease (CHD), cerebrovascular disease and peripheral arterial disease.

Methods: Systematic review of cohort and case-control studies on the association of clinically or radiographically diagnosed PD and ACVD.

Results: Overall, 12 studies were included in this study (six studies on CHD, three studies on cerebrovascular disease, two studies on both coronary heart and cerebrovascular disease mortality and one study on peripheral arterial disease). All but one study reported positive associations between various periodontal disease measures and the incidence of ACVD, at least in specific subgroups. The association was stronger in younger adults and there was no evidence for an association between PD and incident CHD in subjects older than 65 years. Only one study evaluated the association between PD and secondary cardiovascular events.

Conclusions: There is evidence for an increased risk of ACVD in patients with PD compared to patients without. However, this may not apply to all groups of the population. There is insufficient evidence for an association between PD and the incidence of secondary cardiovascular events.

Key words: atherosclerosis; cardiovascular disease; epidemiology; periodontal disease; periodontitis; systematic review

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The possible association between periodontitis (PD) and atherosclerotic cardiovascular disease (ACVD) has received much attention over the past two decades, and a significant number of epidemiological studies have been conducted during this time. The evidence has been systematically reviewed several times during that period (Hujoel 2002, Janket et al. 2003, Khader et al. 2004, Bahekar et al. 2007, Humphrey et al. 2008, Blaizot et al. 2009). Most recently, a comprehensive review was performed by an American Heart Association (AHA) working group (Lockhart et al. 2012), which concluded that "periodontal disease is associated with atherosclerotic

vascular disease independent of known confounders". It further concluded that there was no evidence for a causal link and that, therefore, "statements that imply a causative association between periodontal disease and specific atherosclerotic vascular disease events […] are unwarranted". The review further highlighted several research gaps and methodological issues relevant to further research, including the need for uniform criteria for PD measures and case definitions but mainly with regard to the need of well-designed controlled interventional studies with standard treatment protocols and considerations for issues such as the sustainability of treatment response over time.The aim of this review was to systematically review the evidence for the association between PD and incident ACVD, focusing on the most robust studies in terms of definition of the endpoint (incidence of ACVD) and exposure (clinically or radiographically assessed PD). In light of this evidence, we also discuss some additional issues relevant to further research not discussed in the AHA scientific statement.

Methods

The aim of this systematic review was to evaluate the evidence for an association between PD [defined by clinical attachment loss (CAL) /alveolar bone loss] and the incidence of ACVD For this review, we use the term "atherosclerotic cardiovascular disease" to include atherosclerotic diseases of the heart and the vasculature (coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease).

Objectives and review questions

Primary: What is the association between clinical PD and incident primary or secondary ACVD?

Secondary: What are the modifying effects, if any, of age, gender and smoking?

Eligibility Criteria for Studies

Types of studies

We considered all types of longitudinal studies, either cohort studies or case-control studies. Based on the time and resources available for this review, a pragmatic decision was made to limit this review to studies published in English and German, as these were the languages represented within the team of authors.

Types of exposure measures

To minimize the effect of misclassification of exposure, we only considered studies that employed either periodontal probing to measure periodontal probing depths (PPD) / CAL and/or radiographic assessment of alveolar bone loss. Hence, studies employing self-reported measures of PD or examination findings not based on periodontal probing were excluded. We further excluded studies that used surrogate measures of PD (such as antibody titres to periodontal pathogens) and studies that used composite measures of PD and other oral health conditions (e.g. gingivitis, caries, periapical disease), if the specific effect of PD could not be discerned. Reports had to clearly indicate how dichotomous or categorical definitions of PD were derived.

Types of outcome measures

To compare the risk of ACVD in individuals with PD to the risk of ACDV in patients without PD, we considered studies that evaluated incident CHD (angina, myocardial infarction, CHD death), incident cerebrovascular disease (transient ischaemic attack, stroke) and peripheral arterial disease. For primary disease, patients had to be free of the outcome of interest at baseline (cohort studies) or prior to suffering a cardiovascular event (case-control studies). For example, case-control studies recruiting patients based solely on angiographic findings were not eligible, unless it was specifically stated that angiography was in the context of an incident cardiovascular event. We also considered studies that evaluated the incidence of secondary ACVD events in patients with established ACVD. We did not include studies that used surrogate markers of ACVD (e.g. intima-media thickness, measures of endothelial function) or risk factors for ACVD as outcome measures.

Data presentation/analysis

To qualify for inclusion, studies had to report a measure of relative risk (e.g. risk ratio, rate ratio, hazard ratio, odds ratio) for the association between PD and incident ACVD. As a minimum, studies had to control for the confounding effects of age and gender, either by design (restriction) or statistical analysis (stratification/adjustment). Studies that used matching had to appropriately account for the matching factors in the analysis. We excluded studies where relative risk estimates were not readily interpretable due to inclusion of more than one exposure measure into the same model. For example, we excluded studies that included both a variable for PD status (e.g. none, moderate or severe) and an extent measure (e.g. >4 pockets with PD >4 mm) in the same regression model.

Literature Search

The electronic literature search was designed to be sensitive aiming to identify all relevant cohort and case-control studies (Table 1). Moreover, the references of studies examined for inclusion were thoroughly analysed searching for further studies. We did not actively search the grey literature; this was a pragmatic decision based on the time and resources available for this review.

Review Methods

One single reviewer (P. S.) screened all abstracts to eliminate publications that were clearly irrelevant. The full text of studies that appeared to satisfy the eligibility criteria or where insufficient information was available from the abstract to make a decision was screened by two of four reviewers (C. W., P. S., P. W. and T. D.). Disagreements were resolved by discussion between the reviewers. Data abstraction forms were developed and amended following pilot testing with five studies. Data abstraction was then performed for all full-text papers in duplicate. Disagreements were resolved by discussion. Data were extracted on the general characteristics of the studies in terms of authors, year of publication and country of study as well as population characteristics. Furthermore, specifics regarding exposure assessment and operationalization of PD, if applicable, were abstracted. We

Table 1. Search syntax for articles

Search syntax
1. exp Periodontitis/ or exp Chronic Periodontitis/
2. ("chronic periodont$" or periodont$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
3. 1 or 2
4. exp heart arrest/ or exp myocardial ischemia/ or exp coronary disease/ or exp myocardial infarction/ or exp cerebrovascular disorders/ or exp peripheral vascular diseases/
5. (stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
6. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral$) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral$ or subarachnoid) adj5 (h?emorrhage or h?ematoma or bleed$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. (cardio$ or cardiac or infarction or "coronary heart disease" or "isch$emic heart disease").mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
9. ("peripheral arter$ diseas$" or "peripheral vascular diseas$").mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
10. 4 or 5 or 6 or 7 or 8 or 9

abstracted the relative risk estimates for the full population, and, if reported, any subgroup analyses for age, gender and smoking. If several models with varying levels of confounder control were presented, we chose the estimates from the model with the most extensive control for confounding. No formal assessment of inter-rater reliability was made for any element of data abstraction. Meta-analysis was not attempted because of the significant heterogeneity of studies in terms of virtually all study characteristics, including but not limited to study populations, assessment and definition of the exposure and outcomes and ascertainment and statistical adjustments made for confounders.

Results

The electronic search outlined in Table 1 yielded 1395 potentially eligible records. After screening of titles and, if available, abstracts, 62 full-text articles were reviewed. This resulted in the exclusion of 50 articles, yielding 12 articles for inclusion in this review according to the inclusion/exclusion criteria. The flow of inclusion/exclusion of articles is summarized in Fig. 1. The principle reason for omission of each excluded full-text article is given in Table S1 (available as online supplement). The most common reasons for exclusion of articles were related to studies not evaluating incident ACVD, the exposure measure used (e.g. self-reported diagnosis of PD or composite measures of oral health), or issues with data analysis and presentation.

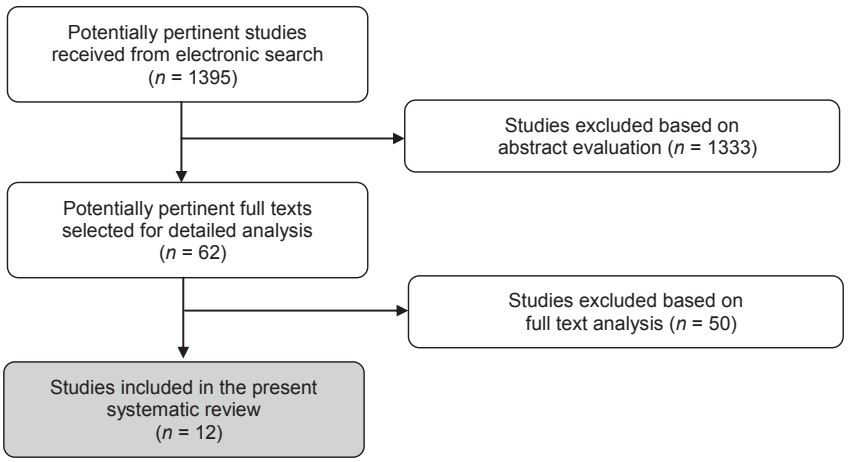

Fig. 1. Selection process of the studies included.

Types of outcomes and studies

We identified three cohort studies and three case-control studies exclusively on CHD (Table S2a), one cohort study and two case-control studies exclusively on cerebrovascular disease (Table S3a) and one cohort study exclusively on peripheral arterial disease (Table S5a). There were two additional cohort studies on ACVD mortality, including both CHD and cerebrovascular disease as causes of death (Table S4a). Tables S2a, S3a, S4a and S5a are available as Online Supplements.

There were several study reports that were based on the same study population but reported on different ACVD outcomes. Data from the Department of Veterans Affairs (VA) Normative Ageing and Dental Longitudinal Studies in Boston, MA, USA were reported in separate publications for CHD (Dietrich et al. 2008), cerebrovascular disease (Jimenez et al. 2009) and peripheral arterial disease (Mendez et al. 1998). Furthermore, the study population sampled for a population based case-control study on myocardial infarction (Andriankaja et al. 2007) was then longitudinally followed up for the incidence of secondary events (Dorn et al. 2010). The latter study was the only study that evaluated secondary cardiovascular events.

Three of the cohort studies (Ajwani et al. 2003b, Tuominen et al. 2003, Xu & Lu 2011) were exclusively on cardiovascular mortality assessed based on linkage of periodontal baseline data with death registry data. All case-control studies were restricted to non-fatal ACVD.

Details regarding the population characteristics of included studies are listed in Tables S2b, S3b, S4b and S5b (available as online only supporting information).

Exposure measurements and operationalization

Exposure measure characteristics of included studies are listed in Table 2. Alveolar bone loss as determined from periapical radiographs was used in all three reports based on the VA Normative Aging Study/Dental Longitudinal Study. All but one study (Mendez et al. 1998) used clinical measures of PD based on periodontal probing (probing depth and/or attachment loss). Partial-mouth recording protocols were utilized in four studies (Ajwani et al. 2003b, Cueto et al. 2005, Sim et al. 2008, Xu & Lu 2011). This included half-mouth recordings of randomly selected quadrants and the use of index teeth, for example, according to Ramfjord and Community Periodontal Index of Treatment Needs (CPITN) protocols.

There was little consistency in terms of the operationalization of PD. Six of the reports used dichotomous PD definitions. These were based on thresholds of either mean CAL (Andriankaja et al. 2007, Dorn et al. 2010), extent scores based on CAL (Cueto et al. 2005), mean bone loss scores according to Schei (Mendez et al. 1998) or based on a minimum number of teeth exhibiting CAL (Sim et al. 2008) or PD (Ajwani et al. 2003b) above a certain threshold (Table 2). Furthermore, studies used either continuous measures of PPD or CAL (Lopez et al. 2002, Dietrich et al. 2008, Jimenez et al. 2009, Dorn et al. 2010), or generated multiple exposure categories based on mean bone loss scores (Dietrich et al. 2008, Jimenez et al. 2009), extent of CAL (Sim et al. 2008), mean of CAL (Grau et al. 2004) or number of teeth exhibiting CAL and/or PD above a certain threshold (Tuominen et al. 2003, Xu & Lu 2011).

Confounder control

In addition to age and gender, all studies included adjusted for a wide range of confounders using statistical modeling (Table 3).

Association between PD and ACVD as represented by incident CHD, cerebrovascular disease and peripheral arterial disease

Relative risk estimates reported in the included studies are listed in Table 3. Overall, with the exception of one study (Tuominen et al. 2003), all studies report significantly higher incidences of ACVD in subjects with PD compared to subjects without PD, or in subjects with more severe PD (worse periodontal status) compared to subjects with no or less severe PD (better periodontal status), albeit not in all subgroups.

There are several studies that report subgroup analyses by age and sex groups. For subgroup analyses by age, cut-offs vary between 60 years (Grau et al. 2004, Dietrich et al. 2008, Sim et al. 2008) and 65 years (Jimenez et al. 2009, Xu & Lu 2011). All studies that stratify by age report stronger associations in younger subjects compared to older subjects. Indeed, for CHD, the majority of studies failed to demonstrate an association between PD and CHD incidence in older subjects. The results with regards to effect-modification by sex are less consistent. Two studies on cerebrovascular disease (Grau et al. 2004, Sim et al. 2008) and one on both CHD and cerebrovascular disease (Xu & Lu 2011) suggest that the association is stronger in men than women, whereas one study on CHD (Andriankaja et al. 2007) found a stronger association in women compared to men and one study found no association between PD and CHD in either sex (Tuominen et al. 2003).

The only study that investigated the incidence of secondary ACVD events found a significant association only in never-smokers, but not in ever smokers (Dorn et al. 2010).

Discussion

This systematic review identified 12 studies that report on the association between clinically or radiographically diagnosed PD and incident ACVD. With the exception of one study (Tuominen et al. 2003), all identified studies report a positive association between PD or PD severity or extent and the incidence of ACVD, at least in selected subgroups, independent of established cardiovascular risk factors. However, the evidence base for an association between PD and peripheral arterial disease, or secondary cardiovascular events in patients who had experienced a cardiovascular event before was very scarce, with only one study addressing each endpoint, respectively.

There is evidence from some studies that the association is stronger in men and younger individuals, although this was not specifically investigated in several of the included studies.

The potential association between PD and ACVD has received much attention in the scientific community since the late 1980s/early 1990s, and several narrative and systematic reviews have summarized the evidence that has emerged over the years, including the pathophysiological pathways that could underpin this association (Kebschull et al. 2010, Lockhart et al. 2012). We therefore chose relatively strict inclusion criteria, focusing on incident ACVD and also focusing on studies that used periodontal probing or radiographic assessment of PD to only include the most robust evidence. The latter criterion is particularly relevant in this field of research, as it excluded studies that used surrogate measures of PD, composite measures or self-reported periodontal measures, excluding several large cohort studies that employed self-reported measures of PD or that were based on the Russell periodontal index. Self-reported PD is associated with significant misclassification, resulting in marked attenuation of relative risk estimates (Dietrich & Garcia 2005).

This review also occasionally highlighted some problems with study design and/or data analysis that reflect the lack of appropriate epidemiological and/or statistical input in design and analysis of the studies. For example, while many of the case-control studies employed matching for some factors in the design, the need to address the

Table 2. Exposure measure characteristics (all studies)

Publication	Method of ascertainment	Partial-mouth recording	Definition(s) of PD(dichotomous)	Other exposure measure
Dietrich et al. 2008	Periapical radiographs (Schei score, ranging from 0 to 5), PPD	N		Categories based on Mean bone loss score, cumulative probing depth [explain in footnote]
Dorn et al. 2010	PPD/CAL	N	Mean CAL $\geq$3 mm	Mean CAL (continuous)
Tuominen et al. 2003	PPD	N		No PPD <4 mm $\geq$1 tooth PPD 4–6 mm $\geq$1 tooth PPD 6+ mm
Andriankaja et al. 2007	PPD/CAL	N	mean CAL $\geq$3 mm	
Cueto et al. 2005	PPD/CAL	Y (Ramfjord teeth only)	% of sites with CAL >3 mm (1) $\leq$ 33% sites No/mild PD (2)>33% moderate and severe PD	
Lopez et al. 2002	PPD/CAL	N		Mean CAL Mean PPD
Jimenez et al. 2009	Periapical radiographs (Schei score, ranging from 0 to 5), PPD	N		Mean bone loss score, Cumulative probing depth [explain in footnote]
Grau et al. 2004	PPD/CAL	N		Stratification into absence of PD or mild PD (defined as mean CAL $\leq$3 mm) and steps of 1.5 mm (mean CAL, 3 to 4.5, 4.5 to 6, and >6 mm). Severe PD: Mean CAL >6 mm.
Sim et al. 2008	PPD/CAL	Y (Two teeth per sextant)	$\geq$1 tooth with $\geq$6 mm CAL	%CAL $\geq$5mm: <48.6%, 48.6%–<73%, $\geq$73%
Xu & Lu 2011	PPD/CAL	Y (Two quadrants, one maxillary and one mandibular)		*Modest PD* One site CAL >4 mm or at least one site with PD >5 mm; *Severe PD* One site with CAL $\geq$6 mm and one or more sites with PD $\geq$5 mm
Ajwani et al. 2003b	CPITN	Y	$\geq$1 pocket $\geq$4 mm (CPITN codes 3 and 4)	
Mendez et al. 1998	Periapical radiographs (Schei score, ranging from 0 to 5)	N	Mean bone loss score >1	

matching in the analysis appropriately was ignored in some studies (Persson et al. 2003). We also had to exclude some studies in which investigators had included more than one measure of PD simultaneously in to the same regression model, rendering the resulting estimates not readily interpretable (Starkhammar Johansson et al. 2008, Pradeep et al. 2010, Holmlund et al. 2011).

The lack of universally accepted recording protocols and criteria for PD classification in clinical research (Tonetti et al. 2005, Page & Eke 2007) is also reflected in the wide variability of criteria evident in this review. Although this variability undoubtedly makes direct comparisons across different studies difficult (and this was one of the main reasons for the authors not to attempt meta-analysis in this review), several points are worthy of consideration. First, it should be noted that the effect of different classification criteria and/or partial-mouth recording protocols on measures of association (where PD is the exposure of interest) is uncertain. This is in contrast to studies on PD prevalence, where for example the underestimation of prevalence associated with partial-mouth recording protocols is well established (Eke et al. 2010). Second, in the context of PD and systemic disease associations, the comparison of results with different PD measures and/or classification criteria may give insight into the underlying mechanisms (Beck et al. 2005). For example, many papers make reference to the fact that the area of the periodontal wound, that is, the ulcerated pocket epithelium is 8–20 cm^2 (Hujoel et al. 2001b). Therefore, measures have been proposed that aim to quantify the size of this wound area (Schwahn et al. 2004, Dietrich et al. 2008, Nesse et al. 2008), such as "cumulative probing depth" utilized in one of the included studies (Dietrich et al. 2008). In contrast, CAL or alveolar bone loss reflect historic disease experience, and may thus be better measures of disease susceptibility rather than current periodontal inflammation. However, comparisons of the results across such dis-

Table 3. Results (all studies)

Publication	Type of Study	Measure of association RR (95% CI)		Factors adjusted for
Dietrich et al. 2008	Cohort	**Mean Bone loss score (MBLS):**		
		Age <60 years		Age, education, income and occupation at baseline and time-varying effects of smoking, body mass index, high density lipoprotein cholesterol, total cholesterol, triglycerides, hypertension, mean systolic blood pressure, mean diastolic blood pressure, diagnosis of diabetes, fasting glucose level, 2 hour glucose level, alcohol consumption and marital status.
		0–≤0.5	HR 1.01	
		(Ref)		
		0.5–≤1	HR 1.7	
		(1.1, 2.5)		
		1–≤1.5	HR 1.6	
		(0.9, 2.6)		
		>1.5	HR 2.1	
		(1.3, 3.6)		
		Edentulous	HR	
		1.9 (0.9, 3.9)		
		Age 60+ years		
		0–≤0.5	HR	
		1.0 (Ref)		
		0.5–≤1	HR	
		0.8 (0.6,1.3)		
		1–≤1.5	HR	
		1.0 (0.7, 1.5)		
		>1.5	HR	
		1.0 (0.6, 1.6)		
		Edentulous	HR	
		1.6 (1.0, 2.7)		
		Cumulative probing depth (CPD):		
		Age <60 years		
		0–<4 mm	HR	
		1.0 (Ref)		
		4–19 mm	HR	
		1.3 (0.8, 2.0)		
		20–40 mm	HR	
		1.4 (0.9, 2.3)		
		41 + mm	HR	
		1.9 (1.2, 3.0)		
		Edentulous	HR	
		1.7 (0.8, 3.6)		
		Age 60+ years		
		0–<4 mm	HR	
		1.0 (Ref)		
		4–19 mm	HR	
		1.1 (0.8,1.6)		
		20–40 mm	HR	
		1.2 (0.8, 1.9)		
		41+ mm	HR	
		0.7 (0.5, 1.2)		
		Edentulous	HR	
		1.7 (0.8, 3.6)		

Table 3. (continued)

Publication	Type of Study	Measure of association RR (95% CI)		Factors adjusted for
Dorn et al. 2010	Cohort	*Never Smokers:* NO PD: (Ref) PD: (0.9, 4.5) Mean CAL (per mm): 1.4 (1.1, 1.9) *Ever Smokers:* Mean CAL (per mm): 1.0 (0.9, 1.2)	 HR 1 HR HR	Age, gender, education, diabetes Age, gender, education, diabetes, cholesterol, lipid medication, hypertensive medication, BMI, physical activity, fruit and vegetable intake
Tuominen et al. 2003	Cohort	*Men:* No PPD 4+ mm: 1.0 (Ref) PPD 4–6 mm: 1.0 (0.6, 1.6) PPD 6+ mm: 1.0 (0.6, 1.6) *Women:* No PPD 4+ mm: 1.0 (Ref) PPD 4–6 mm: 0.9 (0.3, 2.1) PPD 6+ mm: 1.5 (0.6, 3.8)	 HR HR HR HR HR HR	Age, other oral health indicators, education, hypertension, hypercholesterolaemia, smoking, diabetes
Andriankaja et al. 2007	Case-control	*Men:* 1.3 (1.1, 1.6) *Women:* 2.1 (1.5, 2.9) *Never-Smokers:* 1.4 (1.1, 1.9) *Ever Smokers:* 1.5 (1.3, 1.8)	OR OR OR OR	Age, BP, cholesterol, diabetes, BMI, physical activity, smoking Age, sex, BP, cholesterol, diabetes, BMI, physical activity
Cueto et al. 2005	Case-control	No/Mild PD 1.0 (Ref) Moderate/Severe PD 3.3 (1.4, 7.7)	OR OR	Age, sex, smoking, BP, diabetes, cholesterol, regular exercise, [the following were considered but rejected based of 10% rule: BMI, family history CVD, education, social level, residence (urban/rural), employment, marital status]
Lopez et al. 2002	Case-control	Mean PPD: 8.6 (1.2, 61) Mean CAL: 3.2 (1.3, 7.7)	OR OR	Age, sex, diabetes, BP, smoking, [income, job power/prestige, BMI not included in final model but also considered but not associated with outcome $p > 0.25$]

Table 3. (continued)

Publication	Type of Study	Measure of association RR (95% CI)		Factors adjusted for
Jimenez et al. 2009	Cohort	*All Age groups*		Age, BMI, HDL, total alcohol, TG, BP, diabetes, alcohol consumption, smoking, marital status, education, occupation, income.
		Mean Bone loss score:		
		≤0.5	HR	
		1.0 (Ref)		
		0.5–≤1	HR	
		1.7 (0.8, 3.7)		
		1–≤1.5	HR	
		2.3 (1.1, 5.0)		
		>1.5	HR	
		3.5 (1.6, 7.8)		
		Cumulative probing depth:		
		0–<4 mm	HR	
		1.0 (Ref)		
		4–30 mm	HR	
		0.9 (0.5, 1.6)		
		31 mm +	HR	
		1.1 (0.6, 1.9)		
		Age <65 years		
		Mean bone loss score:		
		≤0.5	HR	
		1.0 (Ref)		
		0.5–≤1	HR	
		2.7 (0.8, 9.1)		
		1–≤1.5	HR	
		3.6 (1.0, 13)		
		>1.5	HR	
		5.8 (1.6, 21)		
		Cumulative probing depth:		
		0–<4 mm	HR	
		1.0 (Ref)		
		4–30 mm	HR	
		0.8 (0.3, 2.1)		
		31 mm +	HR	
		1.1 (0.4, 2.8)		
		Age ≥65 years		
		Mean bone loss score:		
		≤0.5	HR	
		1.0 (Ref)		
		0.5–≤1	HR	
		1.1 (0.4, 3.0)		
		1–≤1.5	HR	
		1.5 (0.6, 4.0)		
		>1.5,	HR	
		2.4 (0.9, 6.3)		
		Cumulative probing depth:		
		0–<4 mm	HR	
		1.0 (Ref)		
		4–30 mm	HR	
		0.9 (0.5, 1.9)		
		31 mm +	HR	
		1.1 (0.5, 2.3)		
		All study participants		

Table 3. (continued)

Publication	Type of Study	Measure of association RR (95% CI)		Factors adjusted for
Grau et al. 2004	Case-control	Mean CAL:		
		≤3 mm	OR 1.0	Age, sex, dental visits, PI, missing teeth, caries, BP, diabetes, smoking, alcohol consumption, AF, CHD/PAD, previous stroke/TIA, family history of stroke, education, occupation, father's profession
		(Ref)		
		3–4.5:	OR 1.4	
		(0.8, 2.4)		Age, sex, BP, diabetes, smoking, previous stroke, father' profession, dental visits, number of teeth
		4.5–6:	OR 2.7	
		(1.4, 5.3)		
		>6:	OR 4.3	
		(1.8, 10)		Age, sex, BP, diabetes, smoking, previous stroke,father' profession, dental visits, number of teeth
		Age ≤60 years		
		Mean CAL		
		<=3 mm:		
		(Ref)	OR 1.0	Age, sex, BP, diabetes, smoking, previous stroke,father' profession, dental visits, number of teeth
		3-4.5:		
		(0.8, 2.4)	OR 1.8	
		4.5-6:		
		(1.4, 8.5)	OR 3.4	Age, sex, toothbrushing frequency, dental visits, missing teeth, DMFT, income, education, smoking, alcohol, BP, diabetes, cardiac disease, BMI, family history of BP, DM, cardiac disease
		>6:		
		(1.6, 23)	OR 6.1	
		Age >60		
		Mean CAL		
		<=3 mm:	OR 1.0	
		(Ref)		
		3-4.5:	OR 0.9	
		(0.4, 2.2)		
		4.5-6:	OR 1.7	
		(0.7, 4.5)		
		>6:	OR 1.8	
		(0.6, 5.3)		
		Female		
		Mean CAL		
		≤ 3mm:	OR 1.0	
		(Ref)		
		3–4.5	OR 1.3	
		(0.6, 2.9)		
		4.5-6:	OR 1.7	
		(0.6, 5.3)		
		>6:	OR 1.6	
		(0.3, 8.6)		
		Male		
		Mean CAL		
		≤3 mm:	OR 1.0	
		(Ref)		
		3–4.5:	OR 1.6	
		(0.8, 3.2)		
		4.5-6:	OR 3.4	
		(1.5, 7.7)		
		>6:	OR 4.9	
		(1.9, 13.1)		

Table 3. (continued)

Publication	Type of Study	Measure of association RR (95% CI)		Factors adjusted for
Sim et al. 2008	Case control	No PD: (Ref)	OR 1.0	Age, Sex, toothbrushing frequency, dental visits, missing teeth, DMFT, income, education, smoking, alcohol, BP, diabetes, cardiac disease, BMI, family history of BP, DM, cardiac disease
		PD: (2.3, 7.0)	OR 4.0	
		Based on %extent CAL $\geq$5 mm: No/mild, 0% to <48.6% OR 1.0 (Ref)		
		Moderate, 48.6% to 73% : OR 2.6 (1.4, 4.8)		Sex, toothbrushing frequency, dental visits, missing teeth, DMFT, income, education, smoking, alcohol, BP, diabetes, cardiac disease, BMI, family history of BP, DM, cardiac disease
		Severe, >73%: OR 4.3 (2.3, 8.2)		
		Age 40–59 years CAL <6 mmz OR 1.0 (Ref) CAL $\geq$6 mm OR 6.0 (2.1, 16.8)		
		CAL $\geq$5 mm % 0–48.6% OR 1.0 (Ref)		
Sim et al. 2008 (continued)	Case control	48.8–73%: OR 7.9 (2.2, 29)		Age, toothbrushing frequency, dental visits, missing teeth, DMFT, income, education, smoking, alcohol, BP, diabetes, cardiac disease, BMI, family history of BP, DM, cardiac disease
		$\geq$73%: OR 5.7 (1.9, 17)		
		Age 60–79 years CAL <6 mm OR 1.0 (Ref)		
		CAL $\geq$6 mm: OR 2.6 (1.2, 5.5)		Age, toothbrushing frequency, dental visits, missing teeth, DMFT, income, education, smoking, alcohol, BP, diabetes, cardiac disease, BMI, family history of BP, DM, cardiac disease
		CAL $\geq$5 mm % 0-48.6% OR 1.0 (Ref)		Sex, toothbrushing frequency, dental visits, missing teeth, DMFT, income, education, smoking, alcohol, BP, diabetes, BMI, family history of BP, DM
		48.8–73%: OR 1.4 (0.6, 3.2)		
		$\geq$73%: OR 2.9 (0.9, 5.8)		
		Male CAL <6 mm OR 1.0 (Ref)		Age, race, household income, education, smoking status, alcohol use, total to HDL cholesterol ratio, obesity, diabetes, hypertension and a history of CHD or stroke.
		CAL $\geq$6 mm OR 5.4 (2.4, 12)		
		CAL $\geq$5 mm % 0–48.6% OR 1.0 (Ref)		
		48.8–73%:		

Table 3. (continued)

Publication	Type of Study	Measure of association RR (95% CI)	Factors adjusted for
		OR 2.2 (0.9, 5.5) ≥ 73%: OR 6.4 (2.4, 17) *Female* CAL <6 mm OR 1.0 (Ref) CAL ≥ 6 mm OR 3.8 (1.6, 9.0) CAL ≥ 5 mm % 0–48.6% OR 1.0 (Ref) 48.8–73%: OR 3.8 (1.4, 9.9) ≥ 73%: OR 4.1 (1.6, 11) *Smoking ever* CAL <6 mm OR 1.0 (Ref) CAL ≥ 6 mm OR 7.4 (2.4, 23) CAL ≥ 5 mm % 0–48.6% OR 1.0 (Ref) 48.8–73%: OR 1.8 (0.5, 7.1) ≥ 73%: OR 6.8 (2.0, 24) *Smoking never n = 325* CAL <6 mm OR 1.0 (Ref) CAL ≥ 6 mm: OR 3.3 (1.8, 6.7) CAL ≥ 5 mm % 0-48.6% OR 1.0 (Ref) 48.8-73%: OR 3.4 (1.6, 7.1) ≥ 73%: OR 3.8 (1.7, 8.5) Subgroup analyses for different outcome definitions: *Age 40–59 years* Ischaemic Stroke: OR 25.9 (5.8, 117) Haemorrhagic Stroke: OR 2.3 (0.5, 10.0) *Age 60–79 years* Ischaemic Stroke: OR 2.5 (1.1, 5.7) Haemorrhagic Stroke: OR 2.8 (0.8, 9.7) *Men 30–64 years*	

Table 3. (continued)

Publication	Type of Study	Measure of association RR (95% CI)		Factors adjusted for
Xu & Lu 2011	Cohort	No PD		Age, sex, history of CVD, social class, BMI, smoking, BP, serum cholesterol
		1.0 (Ref)	HR	
		Modest PD		
		1.3 (0.9, 1.7)	HR	
		Severe PD		
		2.1 (1.4, 3.3)	HR	
		65+ years		
		No PD		
		1.0 (Ref)	HR	
		Modest PD		
		1.0 (0.8, 1.2)	HR	
		Severe PD		
		1.1 (0.8, 1.8)	HR	
		Women 30–64 years		
		No PD		
		1.0 (Ref)	HR	
		Modest PD		
		0.9 (0.6, 1.4)	HR	
		Severe PD		
		1.6 (0.7, 3.3)	HR	
		65+ years		
		No PD		
		1.0 (Ref)	HR	
		Modest PD		
		1.0 (0.8, 1.2)	HR	
		Severe PD		
		0.9 (0.5, 1.6)	HR	
		Dentate no PD:		
Ajwani et al. 2003b	Cohort	1.0 (Ref)	HR	
		Dentate PD:		
		2.0 (1.0, 3.8)	HR	Age, sex, BMI, family history of heart disease, smoking
		Edentate:		
		1.4 (0.8, 2.6)	HR	
Mendez et al. 1998	Cohort	No PD:	OR	
		1.0 (Ref)		
		PD:	OR	
		2.3 (1.3, 3.9)		

ACVD, Atherosclerotic Cardiovascular Disease; AF, Atrial Fibrillation; BMI, Body Mass Index; BP, Blood Pressure; CAL, Clinical Attachment Loss; CHD, Coronary Heart Disease; CI, Confidence Interval; CPITN, Community Periodontal Index of Treatment Needs; CVD, Cardiovascular Disease; DM, Diabetes Mellitus; DMFT, Decayed, Missing or Filled Teeth; ECG, Electrocardiogram; HDL, High-Density Lipoprotein; HR, Hazard Ratio, ICD, International Classification of Diseases; MI, Myocardial Infarction; NHANES, National Health And Nutrition Examination Survey; OR, Odds Ratio; PAD, Peripheral Arterial Disease; PD, Periodontitis; PI, Plaque Index; PPD, Periodontal Probing Depth; PVD, Peripheral Vascular Disease; Ref, Reference; RR, Relative Risk, TG, Triglyceride; TIA, Transient Ischaemic Attack.

ease measures have only recently been made (Andriankaja et al. 2007, Dietrich et al. 2008, Jimenez et al. 2009). Third, the fact that the results – across different study types and PD measures – of the studies included in this review are relatively consistent can be seen as reassuring. Interestingly, the authors of one of the included studies also demonstrated in an additional paper that the results across various periodontal measurements and case definitions were remarkably consistent (Andriankaja et al. 2006).

A different but related problem is the impact that missing teeth have on the assessment and operationalization of PD, and subsequently the estimation of PD -ACVD associations. This problem has not been systematically investigated. As PD is a major cause of tooth loss, the resulting misclassification of PD is differential, and depending on the PD measure used may result in over- or underestimation of exposure, with uncertain effects on measures of association. However, measures of the periodontal wound area such as "cumulative probing depth" appropriately account for missing teeth, as the wound area associated with a missing tooth is zero (Schwahn et al. 2004, Dietrich et al. 2008, Nesse et al. 2008).

For CHD and cerebrovascular disease, several cohort and case-control studies were included in this review. Although in theory case-control studies are nested in cohort studies and differ only in using a more efficient sampling strategy (Rothman & Greenland 1998), in practice case-control and cohort studies have different specific strength and limitations. For example, for logistic reasons, case-control studies are typically limited to non-fatal disease but allow the detailed ascertainment and specification of the outcome of interest. In contrast, cohort studies can include both fatal and non-fatal outcomes, but there are often limitations in the level of detail available on the outcomes (e.g. data derived from death certificates). The fact that overall both case-control and cohort studies yielded remarkably consistent results also increases confidence in the reported associations.

Many of the included studies perform age-stratification and, across all studies included in this review, there is consistent evidence that the association between PD and incident ACVD is stronger in younger individuals. Indeed, there appears to be little evidence for any association between PD and CHD in older individuals, which may have important implications for intervention studies as discussed elsewhere in the article. The evidence for effect-modification by gender and smoking is less consistent, although some studies suggest that the association may be stronger in men than women. However, it should be noted that investigators very rarely state whether subgroup analyses were specified *a priori* or whether they were informed by previous analyses (i.e. data driven), raising some concerns regarding the validity of the findings of these subgroup analyses.

Perhaps the most surprising finding of this review was that it included only one study evaluating the association of PD with secondary cardiovascular events, showing a moderate association only in a subgroup of never smokers.

Much of the debate over the past decade regarding the implications of the apparent association between PD and ACVD has obviously been regarding the question whether or not the association is causal, and, if so, whether periodontal treatment in patients with PD can reduce the risk of cardiovascular events. It is widely recognized that the latter question could only be answered by a randomized controlled clinical trial. The significant gaps in our knowledge with regards to this question have also been identified in the recent AHA scientific statement (Lockhart et al. 2012). However, due to the relatively low incidence of ACVD in the general population, it is reasonable to assume that any intervention study would have to be limited to a population with a high absolute risk of a cardiovascular event to be feasible (i.e. affordable). For example, the only pilot interventional study conducted to date, the Periodontitis and Vascular Events (PAVE) study (Beck et al. 2008), was a secondary prevention study, that is, limited to patients with existing ACVD in which the risk of a subsequent cardiovascular event was higher than in the general population. Interestingly, it appears from the findings of this review that the evidence for an association between PD and secondary cardiovascular events, and thus the evidence supporting a secondary prevention trial, is extremely scarce. In addition, since age is the most important predictor of ACVD risk, any high-risk population would be more likely to include older individuals. However, given the weak, if any, association between PD and ACVD in older subjects, an intervention study in a population older than 65 years is not supported by the current epidemiological evidence. In addition to the issues raised in the AHA scientific statement (Lockhart et al. 2012), these findings present yet another formidable challenge for the design and conduct of future clinical trials that aim to address the question of benefits of periodontal therapy on adverse cardiovascular events.

Conclusions and clinical relevance

We conclude that the current evidence supports the notion that the incidence of ACVD, as represented by incident CHD, cerebrovascular disease and peripheral arterial disease is higher in subjects with PD and/or worse periodontal status, compared to subjects without PD or with better periodontal status, independent of many established cardiovascular risk factors. However, this may not be the case in all groups of the population. Further epidemiological evidence is needed to establish if PD is associated with the incidence of secondary cardiovascular events in patients with established ACVD.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1. Full texts excluded including reasons.
Table S2. (a) Outcome Coronary Heart Disease-Study/population characteristics. (b) Outcome Coronary Heart Disease- Demographics.
Table S3. (a) Outcome Cerebrovascular Disease- Study/population characteristics. (b) Outcome Cerebrovascular Disease- Demographics.
Table S4. (a) Outcome cardiovascular and cerebrovascular diseases- Study/population characteristics. (b) Outcome cardiovascular and cerebrovascular diseases- Demographics.
Table S5. (a) Outcome peripheral arterial diseases- Study/population characteristics. (b) Outcome peripheral arterial diseases- Demographics.

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Clinical Relevance

Scientific rationale for the study: Periodontitis has been implicated in the pathogenesis of atherosclerotic vascular diseases.
Principal findings: The incidence of atherosclerotic cardiovascular disease is higher in subjects with periodontitis compared to patients without periodontitis. The association is stronger in younger individuals, and there may be no association in older individuals.
Practical implications: Well-designed epidemiological and interventional studies are required to elucidate the implications of poor periodontal health on atherosclerotic cardiovascular disease risk in different populations.