The relationship between oral and cardiovascular disease: a rapid review

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In brief

(1) There was a firm association between oral health (periodontitis, caries and tooth loss) and atherosclerotic cardiovascular disease (coronary heart disease, stroke, peripheral vascular disease).
(2) There were little or no data to support any links between oral health and other forms of cardiovascular disease (ie non-atherosclerotic such as hypertension, arrhythmias and heart failure).
(3) Periodontal therapy is associated with reductions in surrogate markers of atherosclerotic cardiovascular disease (eg endothelial function, inflammatory and oxidative stress markers).
(4) Oral health promotion improve oral health-related quality of life measures in stroke patients.

Abstract

This review is part of a suite of reviews exploring the relationships between oral health and general medical conditions to support teams within Public Health England and policy makers. The paper aims is to explore whether poor oral health and cardiovascular disease are found in the same individuals or populations, to outline the nature of relationships between them, and to outline the implications of any associations having reviewed the most contemporary evidence in the field. The work was undertaken by four groups each comprising consultant clinicians from medicine and dentistry, trainees and public health and academic staff. The methodology involved a streamlined rapid review process and synthesis of the data. The results identified a number of systematic reviews of low to high quality, which suggests that there is fairly robust evidence that there is an increased risk of atherosclerotic vascular disease [ASVD] among individuals with chronic periodontitis, independent of other established cardiovascular risk factors. And some evidence that the incidence of caries and tooth loss is higher in patients with cardiovascular disease, whilst orofacial pain presents as the sole symptom of stroke in some patients. The findings are discussed in relations to implications for service and future research.

Background

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in the UK, in spite of significant improvements in disease prevention, detection and treatment over recent decades (1). Principle disease categories include (a) atherosclerotic cardiovascular disease (coronary, cerebrovascular and peripheral vascular disease), (b) valvular heart disease, (c) heart failure and cardiomyopathies, (d) arrhythmias, (e) infective and autoimmune conditions (including infective endocarditis), and (f) hypertension.

In 2014, Coronary Heart Disease (CHD) alone was the leading single cause of death in the UK (15% of male and 10% of female deaths, respectively), and accounted for up to 1-in-20 inpatient episodes (2). Cerebrovascular disease (Stroke) resulted in approximately 39,000 deaths in 2014, and was the third largest single cause of mortality in the UK (6% of male and 8% of female deaths). Data from NHS England spending for 2014 reveal that expenditure for CVD was approximately £4.3 billion, with the highest amount (40% or £1.7 billion) arising from 'unscheduled' or emergency care(2). According to the Global Burden of Disease study Ischaemic heart disease is the leading cause of disability years of life lost in England (1)

The two most common diseases affecting oral health are dental caries and periodontitis. Dental caries is the localised destruction of susceptible dental hard tissues by acidic by-products from bacterial fermentation of dietary carbohydrates (3). Periodontitis is a chronic inflammatory disease caused by bacterial infection of the supporting tissues around the teeth(4). Approximately half of all adults in the UK are affected by some level of irreversible periodontitis, which increases with age, and almost a third have obvious dental decay (5).

Several direct and indirect mechanisms have been proposed as pathophysiological links between chronic periodontitis and atherosclerotic cardiovascular disease (6). Key concepts include the interplay between periodontal pathogens, vascular endothelial damage and atherogenesis. Systemic inflammation, with chronically elevated inflammatory markers, is common to both disease processes, though to what extent anatomically remote sources of inflammation interact in causative fashion is unclear. Molecular mimicry may additionally play a role, with evidence of cross-reactivity between oral pathogens and both inflammatory and endothelial cell components. Finally, the direct actions of pathogenic bacteria have also been proposed as a potential explanation for the putative relationship between chronic periodontitis and atheroscelerotic cardio-vascular disease. This has been extensively investigated over recent decades with divergent results, based in no small part due

to difficulties in pathogen detection, proof of causal association and challenges in undertaking clinical outcome studies.

This review was limited to synthesising the literature on the primary links between cardiovascular diseases and oral health. This includes the impact of therapeutic interventions to treat oral disease, but not complications that arise from them; acquired infective endocarditis related to oral disease therapy and cardiac drug-effects (eg gingival hyperplasia in response to dihydropyridines) and their effects on oral health are, therefore, not considered.

Methods

A rapid review of articles published between 2005 and 2015 investigating the relationship between cardiovascular disease and oral health was performed. A rapid review is a synthesis of the most current and best evidence to inform decision-makers [13]. It combines elements of systematic reviews with a streamlined approach to summarise available evidence in a timely manner.

Search syntax was developed based on subject knowledge, MESH terms and task group agreements (Figure 1); followed by duplicate systematic title and abstract searches of three electronic databases: Cochrane, PubMed, OVID (Embase, MEDLINE (R), and PsycINFO). Two independent searches were carried out: screening papers by abstract and title for relevance and duplication. Where there was a large body of evidence regarding a particular element, articles were limited to 2010 onwards to reduce the repetition of evidence.

Figure 1

Studies were included if they were either a systematic review and/or meta-analysis and explored a link between cardiovascular disease and oral health. Disagreements between the reviewers and the wider research group were resolved by discussion. Papers were excluded if they were not available in English, did not mention any term related to oral health or cardiovascular disease, full text not available or related to acquired infective endocarditis related to dental intervention, or drug-induced gingival hyperplasia.

The following information was extracted from each paper: author, year, title, journal, population studied, oral disease/intervention, definitions used, methods, comparison/intervention and controls, outcomes, results, authors' conclusions, quality and quality justification; all shown in the data extraction table

Quality assessment was undertaken for each systematic review using the PRISMA and AMSTAR tools to ascertain risk of bias. An AMSTAR assessment was carried out on all papers with the methodological quality of the review being rated as “High” with a score between eleven and eight, “Moderate” between seven and four, and “Low” between four and zero. The quality of all papers was also assessed by group discussion to reinforce the conclusion reached by the quality score

Results

Overview of the literature

The search identified 247 potentially relevant abstracts, which were screened in duplicate for relevance. Those studies deemed not to have both an oral health and cardiovascular disease component to them were excluded at this stage. The remaining 41 articles were subject to full text review; 23 met the inclusion criteria. A flow diagram of this process is shown in Figure 2. These papers were reviewed and the following themes identified:

Figure 2

Table 1

Quality of the literature

Of the 23 systematic reviews, 17 were found to be high scoring based on AMSTAR tool.

Within the themes identified by this review, most of the papers examined the link between atherosclerotic disease and oral disease and six examined stroke and oral disease. The majority of included papers were rated high quality (6-23), four (24-27) were moderate and one (28) was of low quality based on the AMSTAR rating. For those with less than 11 in the AMSTAR rating, some common quality issues were; lack of bias assessment, lack of publication bias assessment, lack of description of methodological rigour and lack of assessment of publication bias. Quality scores, as well as rationale for these scores, are presented for each paper in the data extraction table (Appendix 6).

Results

The results are reported in seven sections. Each section combines evidence related to cardiovascular disease and its association to an oral disease or an oral disease treatment.

I] Atherosclerotic cardiovascular disease and periodontitis

A number of systematic reviews of observational epidemiologic studies support an association between periodontal disease and atherosclerotic cardiovascular disease, independent of known confounders (6, 13, 23, 24). Dietrich *et al* (2013), found this association was stronger in younger compared with older patients, and in males compared with females. There is a limited evidence base for an association between chronic periodontitis and both the risk of recurrent cardiovascular events in patients with established atherosclerotic disease (secondary events) and peripheral vascular disease, respectively (13). There is no evidence to support or refute a causative relationship between cardiovascular disease and oral health (6).

Five systematic reviews with meta-analyses have demonstrated patients with chronic periodontitis have an increased risk of developing coronary heart disease (7, 8, 15, 18, 23). Helfand *et al* (2009) explored non-traditional cardiovascular risk factors (i.e., those not included within traditional risk models, such as diabetes, blood pressure and cholesterol levels), to explain the risk for incident coronary heart disease (CHD) events in intermediate-risk individuals; chronic periodontitis was one of nine variables studied, but failed conclusively to improve risk prediction(14).

A meta-analysis by Lafon et al. (2014) reported that periodontitis was associated with increased risk of stroke [relative risk 1.63 (1.25, 2.00) (16). Sfyroeras et al (2012), also suggest an association between periodontitis and haemorrhagic stroke; this association was stronger in males, obese patients and non-diabetics (21).

In summary, the evidence suggests that the incidence of atherosclerotic cardiovascular disease is higher in patient with periodontitis compared to those without.

[II] Cardiovascular disease and tooth loss

Four systematic reviews (14-16, 20) suggest that tooth loss is associated with an increased risk of cardiovascular disease, in particular the risk of coronary heart disease and stroke, as outlined below.

a) *Coronary heart disease and tooth loss*

Humphrey *et al* 2008 (15) pooled estimates, demonstrating that individuals with 0-10 teeth had a relative risk of coronary heart disease and coronary death of 1.34 (95% CI 1.10-1.63) compared to patients with 25-32 teeth (p=0.02). A later meta-analysis by Helfand *et* al in 2009 (14) likewise demonstrated a 1.34 relative risk (CI, 1.10-1.63) of general cardiovascular disease for persons with 0-10 teeth compared to those with >10 teeth .

b) Stoke and tooth loss

A meta-analysis by Lafon et al., 2014 (16) indicated a pooled risk estimate of 1.39 (1.13, 1.65) when ischaemic and both ischaemic and haemorrhagic strokes were considered together for edentulous patients compared with dentate patients.

c) Circulatory mortality and tooth loss

Polzer et al., (2012) (20) - 12/ 15 studies reported an increased risk of all-cause mortality among individuals with high numbers of missing teeth; 7/9 studies demonstrated increased circulatory mortality (defined as a primary cardiac cause) in this group.

In summary, although the cause of tooth loss is unclear, the evidence suggests that patients with fewer teeth are more likely to suffer cardiovascular disease and cardiovascular-related death.

IV) Oral facial pain and myocardial infarction

Jalali *et al* (2014) reported on 18 studies (16 case-reports and 2 prospective cohort studies) and showed that isolated craniofacial pain was the sole presenting symptom for acute myocardial infarction in 6% of cases (6:1 ratio of bilateral to unilateral pain, with over 50% of patients in one cohort study reporting throat pain as the most frequently reported location).

In summary, there is evidence of a relationship between isolated orofacial pain and myocardial infarction.

V] *Stroke and oral health related quality of life*

The systematic review by Dai et al 2015 highlights that stroke patients have poorer oral health related quality of life and oral function(11). It is unclear whether this represents disease association or simply a manifestation of reduced dexterity.

In summary, oral health related quality of life of stroke patients is significantly worse than those who have not suffered stroke.

V] Cardiovascular disease and caries/endodontic disease

A systematic review by Dai et al (10), found that patients with stroke have significantly higher caries prevalence [DMFT] scores than healthy controls (10). An earlier systematic review evaluated the potential association between apical periodontitis / endodontic disease and CVD, but found scarce evidence to support this link (28).

In summary, there is evidence that dental caries and disease associated with infections from dental caries or periodontal tissues are associated with incidence of cardiovascular disease.

VII] Stroke and oral health promotion

Two systematic reviews (9, 27), of which one was a Cochrane review (9), show that use of oral health promotion could improve oral health of stroke patients. This includes, periodontal therapy or prophylactic extractions and particularly health care training on oral health promotion

In summary, for patients who have suffered stroke, oral health promotion can have a significant impact on their oral health.

VIII] Cardiovascular disease and periodontal treatment

Periodontal treatment has been shown to have the following effects on surrogate markers implicated in cardiovascular disease: reduction in levels of C-reactive protein. (12, 19, 22, 25), improvement in endothelial function(6, 12), reduction in carotid intima-medial thickness (c-IMT) (Zeng et al 2016).

D'Aiuto et al 2013 reported moderate evidence of a negligible effect of periodontal therapy in reducing interleukin-6 and lipids level, and limited evidence on the effects on the following surrogates: arterial blood pressure, leucocyte counts, fibrinogen, tissue necrosis factor-α, sE-selectin, von Willebrand factors, d-dimers, matrix metalloproteinases, oxidative stress and CVD events. There was no evidence on the effects of periodontal therapy on subclinical atherosclerosis, serum levels of CD40 ligand, serum amyloid A and monocyte chemoattractant protein.

Although periodontal interventions result in a reduction of certain surrogate markers, there is no evidence that this is associated with changes in atherogenesis or disease outcomes (6). This is supported by Li *et al* 2014 who suggest that there is insufficient evidence that periodontal therapy can impact on recurrence of coronary heart disease (17).

In summary there is a large body of evidence suggesting that periodontal therapy has a significant effect on a number of surrogate markers implicated in cardiovascular disease; however, there is insufficient evidence that periodontal therapy has an impact on recurrence or secondary events of coronary heart disease.

Discussion (needs further work)

There is high quality evidence to support an association between cardiovascular disease and oral health most notably chronic periodontitis and atherosclerotic heart disease. This is independent of confounding factors based on evidence from epidemiological studies. However, to date, there has been no causal relationship established between the two diseases (6). The results suggest associations of varied strength between other oral diseases (caries and oral facial pain) and cardiovascular disease.

This review was limited by the widespread discrepancy in the definitions of cardiovascular and chronic periodontitis used in the literature. A review paper by Kelly et al in 2013 highlighted significant structural and methodological variability among the published systematic reviews and meta-analyses regarding the connection between periodontitis and CHD (29). A strength of this review is the high number of meta-analysis which strengthen the evidence.

The findings have significant implications for health services and research. In relation to health services generally, healthcare professionals treating patients with oral diseases or cardiovascular diseases should be aware of the associations between the two diseases and evidence behind their relationship. This will enable them to educate patients and other health professionals.

For oral and dental service, practitioners should provide health promotion advice and signposting for patients presenting with chronic periodontitis in the presence of other cardiovascular disease risk factors such as obesity, diabetes and increased age. Visa Versa patients with cardiovascular disease should be advised by their medical care practitioners to visit dentists to maintain good periodontal health. Dental practitioners should be aware that sole orofacial pain can be a symptom of ischaemic disease.

Patients who have suffered stroke should have an oral health regime provided to aid them to maintain oral health in the event that their dexterity has been altered and any activities to support carers will also be helpful (11).

More sophisticated research is required to establish whether the causal relationship exists between these disease. It is only following this can firm recommendations be made with regards to whether

further interventions are required. Therefore, observational studies should evaluate the association between periodontitis and adverse events in high-risk populations. Randomised controlled trials are required to establish the effectiveness of periodontal treatment in high risk groups on surrogate cardiovascular endpoints.

In summary, there is a firm association between oral health (periodontitis, caries and tooth loss) and atherosclerotic cardiovascular disease, i.e. coronary heart disease, stroke, peripheral vascular disease. There are little or no data to support any links between oral health and other forms of cardiovascular disease, ie non-atherosclerotic such as hypertension, arrhythmias and heart failure. Periodontal therapy is associated with reductions in surrogate markers of atherosclerotic cardiovascular disease such as endothelial function, inflammatory and oxidative stress markers. There is evidence that oral health promotion interventions, involving staff and patients, improves oral health-related quality of life measures in stroke patients.

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Bibliography

1. Newton JN, Briggs ADM, Murray CJL, Dicker D, Foreman KJ, Wang H, et al. Changes in health in England, with analysis by English regions and areas of deprivation, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet. 2015;386(10010):2257-74.
2. Townsend N, Bhatnagar P, Wilkins E, Wickramasinghe K, Rayner M. Cardiovascular Disease Statistics, 2015.2015 12/12/2015. Available from: file:///C:/Users/k1077416/Downloads/bhf-cvd-statistics-2015-final.pdf.
3. Fejerskov O, Kidd E. Dental caries: the disease and its clinical management: John Wiley & Sons; 2009.
4. Eke PI, Page RC, Wei L, Thornton-Evans G, Genco RJ. Update of the case definitions for population-based surveillance of periodontitis. Journal of periodontology. 2012;83(12):1449-54.
5. Steele J, O'Sullivan I. Adult Dental Health Survey2011 21/05/2011. Available from: http://www.hscic.gov.uk/catalogue/PUB01061/adul-dent-heal-surv-firs-rele-2009-rep.pdf.
6. Lockhart PB, Bolger AF, Papapanou PN, Osinbowale O, Trevisan M, Levison ME, et al. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. Circulation. 2012;125(20):2520-44.
7. Bahekar AA, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. Am Heart J. 2007;154(5):830-7.
8. Blaizot A, Vergnes JN, Nuwwareh S, Amar J, Sixou M. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. International dental journal. 2009;59(4):197-209.
9. Brady M, Furlanetto D, Hunter RV, Lewis S, Milne V. Staff-led interventions for improving oral hygiene in patients following stroke. The Cochrane database of systematic reviews. 2006;18(4).
10. Dai R, Lam OL, Lo EC, Li LS, Wen Y, McGrath C. A systematic review and meta-analysis of clinical, microbiological, and behavioural aspects of oral health among patients with stroke. J Dent. 2014;43(2):171-80.
11. Dai R, Lam OL, Lo EC, Li LS, Wen Y, McGrath C. Orofacial functional impairments among patients following stroke: a systematic review. Oral diseases. 2015;21(7):836-49.
12. D'Aiuto F, Orlandi M, Gunsolley JC. Evidence that periodontal treatment improves biomarkers and CVD outcomes. Journal of periodontology. 2013;84(4 Suppl):S85-S105.
13. Dietrich T, Sharma P, Walter C, Weston P, Beck J. The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease. Journal of periodontology. 2013;84(4 Suppl):134008.
14. Helfand M, Buckley DI, Freeman M, Fu R, Rogers K, Fleming C, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151(7):496-507.
15. Humphrey LL, Fu R, Buckley DI, Freeman M, Helfand M. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. J Gen Intern Med. 2008;23(12):2079-86.
16. Lafon A, Pereira B, Dufour T, Rigouby V, Giroud M, Bejot Y, et al. Periodontal disease and stroke: a meta-analysis of cohort studies. Eur J Neurol. 2014;21(9):1155-61.
17. Li C, Lv Z, Shi Z, Zhu Y, Wu Y, Li L, et al. Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis. The Cochrane database of systematic reviews. 2014;15(8).

18. Mustapha IZ, Debrey S, Oladubu M, Ugarte R. Markers of systemic bacterial exposure in periodontal disease and cardiovascular disease risk: a systematic review and meta-analysis. Journal of periodontology. 2007;78(12):2289-302.
19. Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. Journal of clinical periodontology. 2008;35(4):277-90.
20. Polzer I, Schwahn C, Volzke H, Mundt T, Biffar R. The association of tooth loss with all-cause and circulatory mortality. Is there a benefit of replaced teeth? A systematic review and meta-analysis. Clinical oral investigations. 2012;16(2):333-51.
21. Sfyroeras GS, Roussas N, Saleptsis VG, Argyriou C, Giannoukas AD. Association between periodontal disease and stroke. J Vasc Surg. 2012;55(4):1178-84.
22. Teeuw WJ, Slot DE, Susanto H, Gerdes VE, Abbas F, D'Aiuto F, et al. Treatment of periodontitis improves the atherosclerotic profile: a systematic review and meta-analysis. Journal of clinical periodontology. 2014;41(1):70-9.
23. Zeng XT, Leng WD, Lam YY, Yan BP, Wei XM, Weng H, et al. Periodontal disease and carotid atherosclerosis: A meta-analysis of 17,330 participants. Int J Cardiol. 2016;203:1044-51.
24. Azarpazhooh A, Tenenbaum HC. Separating fact from fiction: use of high-level evidence from research syntheses to identify diseases and disorders associated with periodontal disease. J Can Dent Assoc. 2012;78.
25. Freitas CO, Gomes-Filho IS, Naves RC, Nogueira Filho Gda R, Cruz SS, Santos CA, et al. Influence of periodontal therapy on C-reactive protein level: a systematic review and meta-analysis. J Appl Oral Sci. 2012;20(1):1-8.
26. Jalali N, Vilke GM, Korenevsky M, Castillo EM, Wilson MP. The tooth, the whole tooth, and nothing but the tooth: can dental pain ever be the sole presenting symptom of a myocardial infarction? A systematic review. J Emerg Med. 2014;46(6):865-72.
27. Lam OLT, Zhang W, Samaranayake LP, Li LSW, McGrath C. A systematic review of the effectiveness of oral health promotion activities among patients with cardiovascular disease. International Journal of Cardiology. 2011;151(3):261-7.
28. Cotti E, Dessi C, Piras A, Mercuro G. Can a chronic dental infection be considered a cause of cardiovascular disease? A review of the literature. Int J Cardiol. 2011;148(1):4-10.
29. Kelly JT, Avila-Ortiz G, Allareddy V, Johnson GK, Elangovan S. The association between periodontitis and coronary heart disease: a quality assessment of systematic reviews. Journal of the American Dental Association (1939). 2013;144(4):371-9.

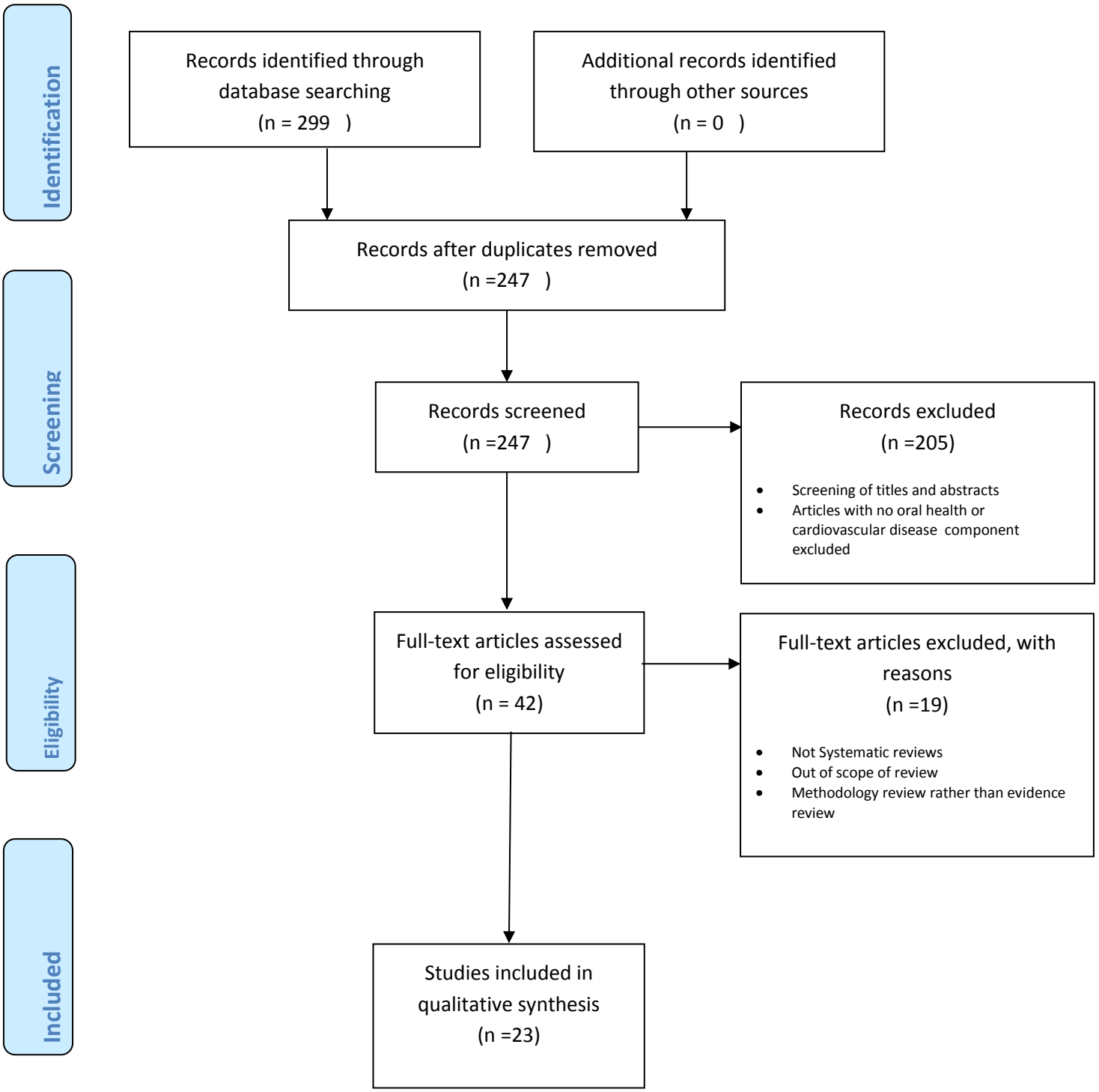
Tables and figures

Figure 1 Search terms

1. acute coronary syndrome.af,
2. angina pectoris.af,
3. angina pectoris.af,
4. angina, stable.af,
5. angina, unstable.af,
6. arrhythmias, cardiac.af,
7. arteriosclerosis.af,
8. arteriolosclerosis.af,
9. atherosclerosis.af,
10. cardiomyopathies.af,
11. cardiovascular diseases.af,
12. cerebrovascular diseases.af,
13. cerebrovasc*.af,
14. cerebrovascular disorders.af,
15. coronary artery disease.af,
16. coronary circulation.af,
17. coronary disease.af,
18. coronary occlusion.af,
19. coronary stenosis.af,
20. coronary thrombosis.af,
21. endocarditis bacterial.af,
22. endocarditis.af,
23. infective endocarditis.af,
24. heart disease.af,
25. heart failure.af,
26. heart valve diseases.af,
27. microvascular angina.af,
28. myocardial infarction.af,
29. myocardial ischemia.af,
30. myocardial ischaemia.af,
31. myocarditis.af,
32. peripheral arterial disease.af,
33. rheumatic heart disease.af,
34. stroke.35. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. dental care.af,
37. dent*.af,
38. dentistry.af,
39. dental caries.af,
40. dry mouth.af,
41. dry socket.af,
42. evidence-based-dentistry.af,
43. geriatric dentistry.af,
44. gingiv*.af,
45. gingiv* .af,
46. gingivitis.af,
47. oral health.af,
48. oral candid*.af,
49. paediatric dentistry.af,
50. periodont*.af,
51. salivary gland.af,
52. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53. 35 and 52
54. systematic review.af,
55. meta analysis.af,
56. meta-analysis.af,
57. 54 or 55
58. 53 and 57
59. remove duplicates from 58
60. limit 59 to humans
61. limit 60 to "review articles"
62. limit 61 to english language
63. limit 62 to yr="2005 -Current"
64. from 62 keep 1,3-6,9

65. from 63 keep 1,3-6,9,12-13,17,19,21-22,26,31,38-39,42,44,50,55,61,65,70,76,81,89,94,97,110,113,115,117,121,132,134,138,141,149,151,153-155,162,164,167,169,171-172,174-176,186,207
66. from 65 keep 1-7,11,13-15,17-23,25-34,36-37,39-47,49-50,52-53

Figure 2 Flow diagram



Author, date and title	Populations included in studies reviewed	Studies Types in Review	Oral disease and diagnostic criteria or Oral disease intervention and description	Cardiovascular disease and diagnostic criteria of	Intervention, comparison	Covariates adjusted	Results	Author's conclusions	Amstar Score	Justification for quality score
Zeng et al. 2016 (23) Periodontal disease and carotid atherosclerosis: A meta-analysis of 17,330 participants	Participants with periodontal disease	15 studies - 5 case–control studies - 10 cross-sectional studies. Studies reported relative risks or odds ratios and their corresponding confidence intervals	Periodontitis- Diagnosis **I)** Clinical attachment loss **II)** Alveolar bone loss **III)** Periodontal pocket death **IV)** CPITN **V)** Gingival index **VI)** Distance between the cemento-enamel junction to bone level	Carotid Atherosclerosis Diagnosis: **I)** Carotid intima thickness (ultrasound) **II)** Carotid plaque thickness(Panoramic radiographs)	Association between periodontal disease and carotid atherosclerosis	Race Age Sex Educational level BP BMI Diabetes Hx of MI Smoking Income, Bleeding on probing Plaque index, LDL HDL HbA1c, Habitual drinking Log-transformed TGLs	**I)** Meta-analysis of 15 studies. Significant heterogeneity among studies (I^2=78.90%;P <0.01) **II)** ORs for the association varied from 1.02 to 5.60. **III)** The overall population with periodontal disease had a significantly **IV)** increased risk for developing carotid atherosclerosis as compared to the reference groups (OR: 1.27; 95% CI: 1.14–1.41; P b 0.001) **V)** Sub –group analysis adjusted for smoking and DM Subgroup analysis of showed borderline significance(OR: 1.08; 95% CI: 1.00–1.18; P = 0.05)	The meta-analysis indicated that the presence of periodontal disease was associated with carotid atherosclerosis; however, further large-scale, well-conducted clinical studies are needed to explore the precise risk of developing carotid atherosclerosis in patients with periodontal disease	11 High	All Amstar questions were satisfied
Freitas et al.2010 (25) Influence of periodontal therapy on C-reactive protein level: a systematic review and meta-analysis	Participants with Periodontal disease	4 RCT s	**Periodontitis** Diagnosis **I)** Minimum of five teeth with a site with attachment >5mm and bone loss in at least two quadrants **II)** 50% of teeth present with PD>6mm and bone loss of >30% **Intensive periodontal treatment in a single session types** **I)** Full mouth instrumentation with manual technique and ultrasound **II)** Positive intensive periodontal treatment	Healthy population Surrogate marker- C-reactive protein	C-reactive protein values before and after periodontal treatment	N/a	**I)** No heterogeneity was observed between the studies (p=0.311) **II).** The general mean Difference in C-reactive protein levels from before to after treatment was -0.231 mg/L, which was a statistically significant result (p=0.000). **III)** Periodontal treatment was seen to be a statistically significant protective factor for the serum levels of C-reactive protein.	Non-surgical periodontal treatment has a positive effect in reducing the serum levels of C-reactive protein, with statistically significant results.	7 (moderate)	Bias not assessed. Conflict of interest not included. Full characteristics of the studies not included.

Helfand et al.2009 (14) Emerging Risk Factors for Coronary Heart Disease: A Summary of Systematic Reviews Conducted for the U.S. Preventive Services Task Force	Participants who had no baseline cardiovascular disease -the investigators adjusted for at least 6 Framingham risk factors examining risk factors	9 systematic reviews **Includes** meta-analysis investigating periodontal disease as a risk factor	**Periodontal disease , tooth loss, gingivitis and bone loss** Physical examination and plain radiography; widely available	No cardiovascular disease	Cardiovascular disease and risk factors ankle–brachial index (ABI), leukocyte count, fasting blood glucose level, periodontal disease, carotid intima–media thickness (IMT), coronary artery calcium (CAC) score as measured by electron-beam computed tomography, serum homocysteine level, lipoprotein(a) level, and C-reactive protein (CRP) level changes in CRP level	Age and sex	**I)** Periodontal disease is an independent, though relatively weak, risk factor for CHD **II)** For cardiovascular diseases in general, relative risk estimates for different categories of periodontal disease ranged from 1.24 (CI, 1.01 to 1.51) for periodontitis to 1.34 (CI, 1.10 to 1.63) for persons with 0 to 10 teeth.	We did not find any direct evidence that periodontal examination would be useful reclassifying persons classified as intermediate-risk by the Framingham risk score.	9 (high)	Only 1 search engine used No assessment of publication bias
Humphrey et al. 2008 (15) Periodontal Disease and Coronary Heart Disease Incidence: A Systematic Review and Meta-analysis	Assessment of periodontal disease, Framingham risk factors, and coronary heart disease incidence in the general adult population without known Coronary Heart Disease	7 cohort studies Meta-analysis undertaken	**Periodontitis Diagnosis-** I). Dental exam; tooth loss II). Radiographic and dental exams: PD,bone loss, clinical probe depth **Number of decayed teeth,** I). Self-reporting	Cardiovascular disease Follow up of CVD Mortality	Periodontal disease and CVD mortality	Age Sex Race Alcohol HDL BP Smoking BMI DM prevalent CHD social class Education Marital status Exercise HTN	**I)** Summary estimate of CHD/CVD death in patients with periodontitis 1.24 (95%CI 1.01–1.51) (P=0.04). **II)** Summary estimate of CHD/CVD death in patients with 0-10 teeth 1.34 95% CI (1.10,1.63 across studies compared with 25-32 teeth(P=0.02) **III)** Relative risk of CHD/CVD death in patients with gingivitis summary estimate was 1.35 (95% CI 0.79–2.30). **IV)** Sub group analysis varied results as follows ***Outcome*** CHD/CVD Death 1.28 (0.94, 1.73) Vs CHD/CVD Events 1.34 (1.08, 1.66)***Gender*** Male 1.23 (0.92, 1.64) Female 1.59 (1.28, 1.96) Both Gender 1.31 (1.08, 1.59) ***Follow Up Length (yrs)*** <= 15 1.19 (1.02, 1.40) > 15 1.67 (1.27, 2.20) ***Risk Factor Measurement*** Dental Exam 1.39 (1.19, 1.62) ***Self Report*** 1.30 (0.96, 1.76) ***Quality*** Good 1.35 (1.06, 1.72) Fair 1.30 (0.97, 1.74)	Periodontal disease is a risk factor or marker for CHD that is independent of traditional CHD risk factors, including socioeconomic status. Further research in this important area of public health is warranted	11 (high)	All AMSTAR questions were satisfied.

Jalali et al. 2014 (26) The tooth, the whole tooth, and nothing but the tooth: can dental pain ever be the sole presenting symptoms of a myocardial infarction	Patients experiencing pain of cardiac origin and had jaw or face pain as their only symptom	18 Studies - 16 case reports -2 prospective cohort studies	Pain in jaw or face	Cardiac ischemia	incidence of odontogenic pain being the sole symptom of cardiac insufficiency	Not reported	**I)** Case studies - the craniofacial pain was reported to be unilateral in seven cases. The other nine case studies cases of bilateral craniofacial pain or did not specify lateralization of the pain. **II)** Prospective cohort studies- 1 study did not specify the locations of craniofacial pain reported by their subjects. 1/2 reported the most frequently reported location of craniofacial pain was the upper throat (81.7%), the left mandible (45.1%), the right mandible (40.8%), and the left temporomandibularjoint/ear region (18.3%).	Based on a single group of studies- isolated craniofacial pain occurs 6% of cases. 6:1 ratio of bilateral to unilateral pain.	8 (moderate)	1 search engine No assessment of publication bias List of excluded papers not included or referenced.
Lafon et al. 2014 (16) Periodontal disease and stroke: a meta-analysis of cohort studies	Participants who were Military men, general public, post-stroke populations.	Nine cohort studies - 8 prospective - 1 retrospective	**Periodontitis** several indicators were combined: periodontitis versus none, pocket depth >3 vs.0–3 mm and bone loss >1.5 vs. <0.5 mm. **Tooth loss** included baseline indicators (edentulousness, number of missing teeth) and incidence of tooth loss **Gingivitis** **Perio assesssment included** - in-depth clinical and radiological exam of loss of attachment and bonesupport for each tooth 1/10. 6/9 used global indicators of oral status , 2/9 self-report	**Type of stroke** -Ischaemic -Haemorrhagic -Neurological deficit **Assessment included** Incident ischaemic strokes were defined using the International Classification of Disease (ICD) in 6/9 studies. Two studies did not use imaging to establish the diagnosis of stroke 1/9 used imaging but it did not apply the ICD classification 2/9 self-reported	Evaluation of the incidence of strokes, evaluation of periodontal status.	**5/9 included all the confounders:** Diabetes, Socio-economic status, Cholesterol, Hypertension	**I) Periodontitis and stroke** - The pooled risk estimate was 1.63 (1.25, 2.00) for ischaemic and ischaemic + haemorrhagic strokes together. **II) Gingivitis and stroke-**The pooled risk estimate was 1.10 (0.77, 1.43) when ischaemic and ischaemic + haemorrhagic strokes were considered together. **III) Tooth loss and stroke** -The pooled risk estimate was 1.39 (1.13, 1.65) when ischaemic and ischaemic + haemorrhagic strokes were considered together.	Results are in accordance with those of previous reviews suggesting a link between stroke and periodontal diseases. More epidemiological and clinical studies are thus needed to clarify the relationship between these inflammatory diseases.	10 (high)	List of excluded papers not included or referenced.

Lam et al. 2011 (27) A systematic review of the effectiveness of oral health promotion activities among patients with cardiovascular disease.	heart transplantation (2 studies), patients diagnosed with hypertension (2 studies), patients with coronary artery disease and/or a previous coronary event (3 studies), and institutionalized patients with a history of stroke (1 study)	8 studies -3 RCT's -3 pre-/post group interventions -1 was a randomized split-mouth study -1 was a quasi-experimental study	**Periodontal health** gingival health, a oral hygiene plaque (7/8) **Changes in c-reactive protein** and IL-6 (1/8)	Patients receiving immunosuppressive therapy following **heart transplantation** (2/8) patients diagnosed with **hypertension** (2/8) patients with **coronary artery disease and/or a previous coronary** event (3/8) Institutionalized patients with a **history of stroke** (1/8).	Effect of oral health promotion which included extractions of poor prognosis teeth, Oral hygiene, root surface debridement, antibiotic gel, antibiotics following oral health promotion.	Not reported	**I) Immunosuppressive therapy following heartTransplantation-** significant decrease in BOP following oral hygiene instructions, scaling, and root planing. **II) history of stroke-**significant reduction in denture plaque at 1 and 6 months following the administration of an oral health care education program. **III) hypertension-intervention** involving oral hygiene instructions and scaling significantly improved periodontal health. **IV) coronary artery disease or a recent coronary event-** Subjects receiving "intensive treatment" were found to have significantly lower mean probing depths, extent probing depths, extent attachment loss, and extent subgingival calculus compared to the control group at 6 months.	Oral health education with no other clinical intervention improved denture plaque scores in stroke patients. Oral health promotion activities in a clinical setting with CVD patients can result in improvements in periodontal health.	7 (moderate)	No evidence of scientific testing of studies. No mention of the methodological rigor and scientific quality No assessment of publication bias. List of excluded papers not included or referenced.
.Li et al.2014 (17) Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis	Participants with 50%blockage of one coronary artery or have had a coronary event within three years with periodontal disease	One RCT included	**Periodontal disease** Diagnosed -six natural teeth, including third molars, with at least three teeth with probing pocket depth ≥ 4 mm, at least two teeth with interproximal clinical attachment loss ≥ 2mm, and ≥ 10% of sites having bleeding on probing	50% blockage of one coronary artery or have had a coronary event within three years	Effect on effect of SRP and community care in reducing the risk of CVD recurrence in patients with chronic periodontitis ;effects of SRP compared with community care on high-sensitivity C-reactive protein (hs-CRP); the number of patients with high hs-CRP and adverse events	n/a	**I)** Insufficient evidence to determine the effect of SRP and community care in reducing the risk of CVD recurrence in patients with chronic periodontitis (risk ratio (RR) 0.72; 95% confidence interval (CI) 0.23 to 2.22; very low quality evidence). **II)** The effects of SRP compared with community care on high-sensitivity C-reactive protein (hs-CRP) (mean difference (MD) 0.62; -1.45 to 2.69), the number of patients with high hs-CRP (RR 0.77; 95% CI 0.32 to 1.85) and adverse events (RR 9.06; 95% CI 0.49 to	Insufficient to determine the effect of periodontal treatment on CVD in patients with chronic periodontitis.	11 (high)	All AMSTAR questions were satisfied

							166.82) were also not statistically significant.			
Mustapha et al.2007 (18) Markers of Systemic Bacterial Exposure in Periodontal Disease and Cardiovascular Disease Risk: A Systematic Review and Meta-Analysis	men 45 yrs - 74 yrs old in USA, Japan, Finland and Sweden	10 selected publications included in systematic review. These 10 publications contained - 12 separate studies, both cohort and cross-sectional -14 separate analyses that could be combined in meta-analysis. -1 study was excluded in the meta-analysis	**Periodontal disease** **Diagnosis** CPITN. - Probing depth, bleeding on probing - plaque scores - Attachment loss	**Cardiovascular outcome including-** -CV mortality -Fatal/non-fatal MI -Stroke -Prevalent CHD -CIMT **Diagnosis** CVD was determined in 9/10 of the studies by International Classification of Diseases, Ninth Revision codes.1/10 ARIC study	Presence of clinical periodontal disease with elevated systemic markers of periodontal related bacterial exposure(*Porphyromonas gingivalis* (Pg), and *Actinobacillus actinomycetemcomitans (Aa))* and risk of developing cardiovascular outcomes	All except three studies matched or adjusted for "all the traditional cardiovascular risk factors".	**I)** the higher level of exposure was not associated with CVD (average OR, 1.36; 95% CI: 0.96 to 1.93; P = 0.089) **I)** periodontitis was associated significantly with CHD, with an average OR of 1.75 (95% CI: 1.32 to 2.34; P <0.001) **II)** This group was not associated with CVD events or with stroke but was associated with a significant increase in mean CIMT (0.03 mm; 95% CI: 0.02 to 0.04).2.34; P<0.001)	Periodontal disease with elevated bacterial exposure is associated with CHD events and early atherogenesis (CIMT), suggesting that the level of systemic bacterial exposure from periodontitis is the biologically pertinent exposure with regard to atherosclerotic risk.	11 (high)	All AMSTAR questions were satisfied
Paraskevas et al. 2008 (19) A systematic review and meta-analyses on C-reactive protein in relation to periodontitis	Participants with diagnosed periodontal disease	13 studies included in met-analysis - 11 case-control -2 intervention studies	**Periodontal disease** **Diagnosis** -clinical exam Interproximal attachment loss, bleeding on probing. Pocket depth, radiographs	Effect on C-reactive protein in healthy participants	Difference in CRP levels between perio and healthy controls And effect of non-surgical periodontal therapy, periodontal surgery including giving antibiotics for 4 days	Some were not reported Age, Gender, Race, Smoking, Education, BMI, HTN, Cholesterol, Positive CMV	**I)** There was a statistically significant WMD (1.65 mg/l; 95% CI 1.05–2.24; po0.00001) in CRP levels between the periodontitis patients and controls. **II)** Periodontitis elicits a mild acute-phase response with elevation of CRP levels compared with healthy controls. Periodontal treatment results in lowered CRP levels; however, the treatment studies available are scarce	There is strong evidence from cross-sectional studies that plasma CRP in periodontitis is elevated compared with controls. There is modest evidence on the effect of periodontal therapy in lowering the levels of CRP	11 (high)	All AMSTAR questions were satisfied

Polzer et al.2010 (20) The association of tooth loss with all-cause and circulatory mortality. Is there a benefit of replaced teeth? A systematic review and meta-analysis	General population	Includes 25 cohort studies -Tooth loss 17 included in qualitative synthesis -Denture use 6 studies in qualitative synthesis 2 studies in quantitative synthesis	Tooth loss, number of teeth, dental disease	Circulatory mortality	Whether the number of teeth is related to all-cause or circulatory mortality and whether replaced teeth are protective against all-cause or circulatory mortality.	Age, Sex, Socioeconomic status, Marital status, smoking, alcohol consumption, physical activity, diabetes, obesity, triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, hypertension, oral health behaviour, periodontitis and caries	**I)** Number of teeth and circulatory mortality-12 / 15 studies reported an increased risk of unspecific death among women or men with higher numbers of missing teeth, while 7/9 studies revealed increased circulatory mortality. **II)** **Denture use and all-cause mortality**-No study particularly investigated whether the number of replaced or un-replaced teeth affects mortality. An effect of denture use on circulatory mortality remains to be established, as well as how the number of replaced teeth affects mortality. **III)** The findings of two moderate studies indicated an effect of prosthodontic replacements on all-cause mortality, which was supported in bias analysis.	An effect of denture use on circulatory mortality remains to be established, as well as whether the number of replaced teeth affects mortality. Specifying the role of potential pathways by which tooth loss-related mortality is mediated will possibly increase the value of dental treatment for general health.	10 (high)	One search engine
Sfyroeras et al.2012 (21) Association between periodontal disease and stroke	Participants who have suffered stroke and non-stroke controls participants	17 cohort studies -6 prospective -7 retrospective	Periodontal disease -self reported -loss of teeth -radiographic -Pocket probing depth	cerebrovascular ischemia, ischaemic stroke, TIA, non-stroke control subjects	risk of stroke in patients with periodontitis vs control group -those without periodontitis	Gender, Race, Education, Sex, Poverty index, HTN, Diabetes, Cholesterol, BMI, Smoking, Alcohol	**I)** Periodontitis is independently associated with a nonfatal haemorrhagic stroke (OR, 2.4; 95% CI, 1.1-5.5) after controlling for possible potential confounders. **II)** The association between periodontitis and haemorrhagic stroke was stronger among males, patients without diabetes mellitus, and obese patients.	There is evidence that periodontitis is associated with increased risk of stroke. However, the results of this meta-analysis should be interpreted with caution because of the heterogeneity of the studies as well as the differences in periodontitis definition.	9 (high)	1 search engine used Excluded studies not listed

Teewu et al. 2014 (22) Treatment of periodontitis improves the atherosclerotic profile: a systematic review and meta-analysis	Healthy populations, populations with co-morbidities	25 RCTs / Clinical controlled trials.	**Periodontal disease**	Outcome variables must be clinical CVD parameters (i.e. clinical event, such as angina pectoris, myocardial infarction, stroke, death) and/or markers related to atherosclerosis and CVD risk, including markers of systemic inflammation and thrombosis, lipid and glucose metabolism and vascular function.	**Intervention group** receiving PT and a non-intervention group receiving no periodontal Treatment (NPT). Comparing impact of periodontal treatment, root surface debridement on CRP levels, fibrinogen and total cholesterol.		Meta-analyses demonstrated significant weighted mean difference for: **I)** hsCRP (0.50 mg/l, 95% CI: 0.78; 0.22) **II)** IL-6(0.48 ng/l, 95% CI: 0.90; 0.06) **III)** TNF-a (0.75 pg/ml, 95% CI: 1.34;0.17) **IV)** Fibrinogen (0.47 g/l, 95% CI: 0.76; 0.17) **V)** Total cholesterol (0.11 mmol/l, 95% CI: 0.21; 0.01) **VI)** HDL-C (0.04 mmol/l, 95% CI: 0.03;0.06) **all favouring periodontal intervention.**	Periodontal treatment improves endothelial function and reduces biomarkers of atherosclerotic disease, especially in those already suffering from CVD and/or diabetes.	11 (high)	All AMSTAR questions were satisfied
Azarpazhooh 2012 (24) Separating Fact from Fiction: Use of High level evidence from research synthesis to Identify Diseases and disorders associated with periodontal disease	Not stated	15 SRs and Meta-analysis, of these 6 reviews of CVD and Periodontitis Six meta-analyses published between 2003 and 2009 showed a.	Variety of measures of periodontal disease including: Gingivitis or Periodontitis. Periodontal disease with elevated systemic markers of periodontal related bacterial exposure, as measured by periodontal bacterial burden, periodontitis specific serology or C-reactive protein. Periodontal disease (periodontitis, tooth loss, gingivitis and bone loss)	Cardiovascular disease > no specific information given regarding diagnostic criteria.	Association between periodontal disease and cardiovascular disease, through pooled analysis	Not mentioned	**I) association between CVD and periodontal disease or gingivitis** R. R 1.19(95% CI 1.08–1.32) **For** patients ≤ 65 yearsof age only: RR 1.44(95% CI 1.20–1.73)**For** patients with nonhemorrhagic stroke only: RR 2.85 (95% CI 1.78–4.56)(1/6) **II)** CHD: RR 1.15 (95% CI 1.06–1.25) CVD: RR 1.13(95% CI 1.01–1.27) (1/6) **III)** RR 1.14(95% CI 1.07–1.21)OR 2.22(95% CI 1.59–3.12)Prevalence difference: OR 1.59 in (95% CI 1.33–1.91)Patients with< 10 teeth only:RR 1.24 (95% CI 1.14–1.36) (1/6) **IV)** CHD: OR 1.75 (95% CI 1.32–2.34) Mean CIMT difference: 0.03 mm (95%	Individuals with periodontitis have a significantly higher risk of various other problems, including cardiovascular disease, diabetes mellitus, respiratory disease and preterm low-birth-weight deliveries. However the paper recognises the lack of heterogeneity within the available studies in particular in relation to the way in which periodontal disease is reported/ diagnosed.	7 moderate	Methodology not clear. No clear inclusion / exclusion criteria. Single reviewer. Single database used for search

			Clinical exposure measurements related to periodontal disease				CI 0.02–0.04) Stroke: no association.(1/6) **V)** Any CHD or CVD event:RR 1.24 (95% CI 1.01–1.51)All CHD and CVD events: RR 1.34 (95% CI 1.10–1.63).(1/6) **VI)** OR 2.35 (95% CI 1.87–2.96)RR 1.34 (95% CI 1.27–1.42) (1/6) **VII)** Periodontal treatment had no effect on serum levels of C-reactive protein (CRP; a surrogate risk marker for CVD) at 2 months after the treatment. Therefore, it appears that periodontal therapy has no consistent effect on CRP levels, which couldlead to the conclusion that CVD would not bereversed by periodontal treatment			
Bahekar et al. 2007(7) The prevalence and incidence of coronary heart disease is significantly increased in periodontitis. A meta-analysis	25-84 age range, more men than women, largest study looked at male health professional aged 40-75. 41119 in study.	- 5 Prospective cohort studies (follow-up >6 years - 5 case-control studies - 5 cross-sectional studies that were eligible for meta-analysis	**Periodontal disease** either by **I)** Clinical assessment of oral health (includes probing depth, periodontal pocket bleeding index, plaque index, modified CPITN, , clinical attachment level and radiographic analysis of bone levels) **II)** Self-reported periodontal disease **Gingivitis** With or without pockets, grade 4	**Coronary heart disease** Studies defining cases as people with fatal or nonfatal coronary artery disease (CAD): (ischaemic stroke was included due to its presence in some of the studies & pathophysiology which differs from haemorrhagic stroke) **Assessments in studies were:** Medical records of MI, CABG, Serum enzyme levels, ECG, angiography, BP,	Patients with and without periodontal disease and relative risk or of having CHD	Age, sex, race, BMI, systolic BP, education, poverty, diabetes, marital status, smoking, physical activity, alcohol, cholesterol socioeconomic status, HTN, diabetes, serum lipids, number of previous MI, race, aspirin or β-carotene treatment assignment,	**I). .**Meta-analysis of 5 prospective cohort studies (86092 patients) indicated that individuals with PD had a higher risk of developing CHD than the controls (relative risk 1.14, 95% CI 1.074-1.213, P b .001). **II)** The case-control studies (1423 patients) showed an even greater risk of developing CHD (OR 2.22, 95% CI 1.59-3.117, P < .001). **III).** The prevalence of CHD in the cross-sectional studies (17724 patients) was significantly greater among individuals with PD than in those without PD (OR 1.59, 95% CI 1.329-1.907, P < .001). **IV)**No. of teeth and incidence of CHD was RR 1.24 (95% CI 1.14-1.36, P b .0001) of development of CHD in patients with <10 teeth	This meta-analysis indicates that both the prevalence and incidence of CHD are significantly increased in PD. Therefore, PD may be a risk factor for CHD. Prospective studies are required to prove this assumption and evaluate risk reduction with the treatment of PD	high (10)	No mention of source of funding / conflict of interest

				Cholesterol values, self-reported MI, History of revascularization , Non-fatal MI (WHO criteria)						
Blaizot 2009 (8) Periodontal disease and cardiovascular events meta-analysis of observational studies	patients with and without periodontal disease from varied studies which included NHANES studies, ARIC and other studies, Subjects were men and women, mean ages between 52-59	- 7 cohort, - 22 cross-sectional and case-control studies)	No stated diagnostic criteria for periodontal disease. Studies included periodontitis diagnosed by variety of clinical methods, also included diagnosis of periodontitis based on patient questionnaire.	Cardiovascular diseases as confirmed by one of the following criteria: diagnosed coronary artery disease, angina pectoris, acute myocardial infarction, mortality caused by cardiac pathology	Patients with periodontal disease and those without periodontal disease	Age Sex Race Smoking Status Diabetes Blood pressure BMI Hypertension Hyperlipidemia CAD Income level Civil status Education CHD Hypertension Serum cholesterol Serum Triglycerides Alcohol Life situation Marital status Hypercholesterolemia Obesity Current dentist CHD family history Diet CRP Leukocytes Social class Place of birth Exercise Total pack-years Unemployment Hobby Plaque Poverty index Physical activity Husband's occupational category combined income	**I)** The pooled odds ratio calculated from the 22 case-control and cross-sectional studies was 2.35 (95% CI [1.87; 2.96], p< 0.0001). II) The risk of developing cardiovascular disease was found to be significantly (34%) higher in subjects with periodontal disease compared to those without periodontal disease (pooled relative risk from the 7 cohort studies was 1.34 (95% CI [1.27; 1.42], p< 0.0001).	From observational studies that subjects with periodontal diseases have higher odds and higher risks of developing cardiovascular diseases but the reduction in the risk of cardiovascular events associated with the treatment of periodontitis remains to be investigated.	high (11)	All AMSTAR questions were satisfied
Brady et al. 2006 (9)	Patients with a diagnosis of stroke receiving	3 RCTs	**Oral hygiene** **I)** Dental plaque: plaque scale **II)** Denture plaque:	Patients post stroke	**Interventions: I)** OHC education training programme (n=67) **II)**Decontamination gel	n/a	**I). OHC training intervention versus standard care** ***Dental plaque*** There was no evidence of a	The little evidence that is available suggests that even an hour-long training	11 High	All AMSTAR questions were satisfied

Staff led interventions for improving oral health for patients following a stroke (Cochrane review)	assisted oral care within a healthcare facility.(included, nursing homes) N=470		denture cleanliness scale **Oral hygiene interventions**- Broad categories included **I)** Assessment tool. **II)** Equipment (for example, toothbrush). **III)** Agent (for example, mouthwash). **IV)** Staff training. V) Oral hygiene promotion.		(n=203) **III)**OHC- augmented ventilator associated pneumonia bundle of care (n=200) **Controls** **I)** placebo gel **or** **II)** standard care		difference between the percentage of dental plaque tooth coverage observed amongst the residents whose carers had been offered training and those whose carers had not ***Denture plaque*** 1 month after training those in homes that had received the intervention had less plaque on their dentures than those receiving usual oral care (DMS -1.31, 95% CI -1.96 to -0.66, P < 0.0001). (1.2.2) This difference could still be observed six months after the training intervention (DMS -1.57, 95% CI -2.23 to -0.92, P < 0.00001). **II) Staff knowledge** (P = 0.0008) and attitudes (P = 0.0001) towards oral care also improved. **III) The decontamination gel reduced the incidence of pneumonia amongst** the intervention group (OR 0.20, CI 95% 0.05 to 0.84, P = 0.03	session delivered by a dental health professional can change healthcare staff's knowledge of and attitude towards administering oral care and may have a positive impact on patients' oral hygiene as measured by denture cleanliness. There is some evidence that, despite an attendance rate of only two-thirds of the healthcare staff and a high staff turnover rate characteristic of such settings, the benefits of training were not only retained but appeared d to be successfully transferred d to new members of staff.		
Lockhart et al.2012 (6) Periodontal Disease and Atherosclerotic Vascular Disease: Does the Evidence Support an Independent Association?	Adult population	A total of 537 peer reviewed publications including: clinical studies, systematic reviews, animal studies, and articles of material importance to the subject of this report	Periodontal disease	Atherosclerotic cardiovascular disease	periodontal interventions systemic inflammation and endothelial dysfunction	Age; race or ethnicity; sex; socioeconomic status (income and/or education); smoking habits; (6) diabetes (presence or duration/haemoglobin A1c); hyperlipidaemia (or low-density lipoprotein cholesterol and/or high-density lipoprotein cholesterol and/or triglycerides); (hypertension (or systolic and/or diastolic blood	**I)** Observational studies to date support an association between PD and ASVD independent of known confounders. **II)** They do not, however, support a causative relationship. **III)** Although periodontal interventions result in a reduction in systemic inflammation and endothelial dysfunction in short-term studies, there is no evidence that they prevent ASVD or modify its outcomes.	Extensive review of the literature indicates that PD is associated with ASVD independent of known confounders. This information comes mostly from observational studies. Statements that imply a causative association between PD and specific ASVD events or claim that therapeutic interventions may be	High (10)	Only one database used for search

						pressure); body mass index or waist/hip ratio or obesity; alcohol consumption; physical activity;marital status; microalbuminuria; C-reactive protein; fibrinogen; (diet; vitamin E intake; statin intake; (history of ASVD; family history of ASVD; current access to dentist; renal disease; papillary bleeding score; dependent living; hypertension medication; frequency of dental visits; oral hygiene; missing teeth; DMFT index (decayed, missing, filled teeth); family history of diabetes; and family history of hypertension. §Ischemic and hemorrhagic stroke.		useful on the basis of that assumption are unwarranted		
Cotti et al.2011 (28) Can a chronic dental infection be considered a cause of cardiovascular disease? A review of the literature	5 studies mentioned of male and female participants	5 epidemiological studies	Apical periodontitis. Pulpal inflammation requiring endodontic treatment.	Coronary heart disease	Not specified	Articles mentions that studies after 'adjustment for covariates of interest' actual variables not highlighted	**I)** The potential CV consequences of apical periodontitis/endodontic disease remain largely unknown and controversial. **II)**The results in the 5 studies looked at were unequivocal	Only a more focused and rigorous scientific research can determine a definitive opinion on the Relationship between endodontic disease and CVD. Therefore it would be important to use dental infection as an independent variable in future CVD research.	Low (3)	No clear description of method used in inclusion / exclusion criteria. No record of multiple researchers.

Dai et al.2014 (10) A systematic review and meta-analysis of clinical, microbiological, and behavioural aspects of oral health among patients with stroke	Studies of patients with stroke	20 papers. observational studies	**I) Tooth loss.** **II) Oral hygiene and gingival condition** bleeding index and plaque index. **III)Periodontal condition** measured by clinical attachment / probing depths. Periodontal pathogens. **IV)Caries** DMFT. **V) Behavioural aspect**: Attendance patterns. **VI)Microbiological and immuno- logical attributes:** Oral biomarkers Oral opportunistic pathogens	patients with a previous diagnosis of stroke	differences in standardized mean values of the DMFT oral hygiene status – plaque index and gingival index , periodontal health status – clinical attachment loss and probing depth and dental attendance for patients with stroke compared to control groups	Not highlighted	**I)**The standardized mean differences of the parameters (fixed effect, randomeffect model) for patients with stroke compared to control groups were: **number of teeth** (0.325, 0.271), **II)DMFT** (0.246, 0.246), oral hygiene status – plaque index (0.305, 0.356) **III) Gingival index** (0.716, 0.653), **IV) periodontal health** status – *clinical attachment loss* (0.437, 0.490) *probing depth* (0.470, 0.579). **V)**a lower chance of dental attendance was observed among patients with stroke (OR:0.493,0.480) **VI)Microbiological and immuno-logical attributes:** Two studies isolated *Porphyromonas gingivalis* and *Aggregati-bacter-actinomycetemcomitans* from either subgingival plaque26 or saliva.36 There was no consistent finding regarding whether there is significant difference in the prevalence of the two periodontal pathogens between patients with stroke and the controls. Inconclusive results re **oral biomarkers**. And 1 study identify candida albicans as most prevalent yeast post stroke. Anaerobic gram negative significantly decrease longer post stroke	Patients with stroke had a poorer oral health status in terms of greater tooth loss, more dental caries experience and poorer periodontal health status than healthy controls. Coupled with this, people with stroke are less frequent dental attenders. Although colonization by opportunistic pathogens was common among patients with stroke, lack of control group comparisons and variations in sampling methods precluded definitive microbiological conclusions to be drawn.	High (11)	All AMSTAR questions were satisfied
Dai et al.2015 (11) Orofacial functional impairments among patients following stroke: A systematic review	Patients with stroke and without stroke: Studies with patient controls with clinical oral health measures (13/23) were either in the	18 Observational studies - prospective, - case–control, - cross-sectional studies reporting either objective or subjective outcomes for orofacial	**I)** lip force **II)** salivary flow rate **III)** chewing performance **IV)** Oral health related quality of life measured by OHIP, GOHAI and OHIP EDENT	Patients that have suffered a stroke	Comparing lip force, salivary flow rate, and chewing performance of patients with stroke with the healthy controls	Not mentioned	Patients with stroke consistently showed a decreased lip force, salivary flow rate, and chewing performance compared with the healthy controls. Due to equivocal results gained from the effective papers, the qualitative assessments regarding whether there was any change in masticatory force	Existing evidence highlights a number of orofacial functional impairment experienced by patients following strokes, which include decreased salivary flow, lip force, and chewing efficiency. One paper	High (11)	All AMSTAR questions were satisfied

	population or in hospital (5/13)	functional impairments among patients with stroke.					on the affected side and oral health-related quality of life were inconclusive.	suggested that stroke may have sustained effects on some orofacial functions, with spontaneous recovery unlikely to occur. Rehabilitative approaches, with the aim of promoting orofacial functional recovery, deserving further consideration in future Studies.		
Dietrich et al. 2013(13) The epidemiological evidence behind the association between periodontitis and incident atherosclerotic cardiovascular disease	Patients with clinically or radiographically diagnosed PD + incident ACVD. Younger adults only, relationship between PD and CVD not observed in adults over 65 years of age	- 12 Longitudinal studies. - 7 cohort studies. - 2 case controlled studies. **CHD.** 3 cohort studies. 3 case-control **cerebrovascular Disease.** 1 cohort study 2 two case control **peripheral arterial disease** 1 cohort study on **ACVD mortality, including both CHD and cerebrovascular disease as causes of death.** 2 cohort studies	Periodontal disease defined as clinical attachment loss / alveolar bone loss. Only studies involving periodontal probing or radiographic bone loss to assess periodontal disease included	Atherosclerotic cardiovascular disease, to include atherosclerotic diseases of the heart and the vasculature including (coronary heart disease, cerebrovascular disease, peripheral arterial disease.	Comparison of the risk of atherosclerotic cardiovascular disease in individual's with periodontal to disease to individuals without. Incidence of secondary ACVD events in patients with established ACVD. Studies assessing surrogate markers of ACVD or risk factors of ACVD as outcome measures not included.	All studies adjusted for a variety of cofounders including: Age Sex BMI Family history of heart disease Smoking Social class Blood pressure Serum cholesterol Tooth-brushing frequency Dental visits DMFT	Relative risk estimates reports in 11 /12 studies report significantly higher incidences of ACVD in subjects with PD compared to subjects without PD. Stronger association in younger subjects compared to older subjects. One study investigated incidence of secondary ACVD events found a significant association in never-smokers, but not in ever smokers.	Incidence of ACVD as represented by incident CHD, cerebrovascular disease and peripheral arterial disease is higher in subjects with Periodontal disease and or worse periodontal status compared to subjects without periodontal disease or with better periodontal status. Younger adults only, relationship between PD and CVD not observed in adults over 65 years of age > Independent of established cardiovascular risk factors.	High (9)	Only one primary searcher / reviewer Search databases not specified.

D'Aiuto. 2013 (12) Evidence that periodontal treatment improves biomarkers and CVD outcomes	Studies where Individuals had to have periodontitis, but the type of disease was not limited Follow-up time ranged from 6 to 24 weeks. Studies had similar response variables.	89 studies for qualitative synthesis 14 studies in quantitative synthesis	Periodontitis is a chronic inflammatory disease affecting the periodontium and resulting in progressive attachment and alveolar bone loss	cardiovascular diseases (CVDs) biomarkers and outcomes	Effects of periodontal therapy on traditional CVD risk factors including: Lipids and Blood pressure Effects of periodontal therapy on CVD surrogate and hard endpoints including: Endothelial function Subclinical atherosclerosis – carotid intima–media thickness Cardiovascular mortality/morbidity Effects of periodontal therapy on novel CVD risk factors: including various Inflammatory markers	Not mentioned for specific studies included	**I)** no evidence on the effects of periodontal therapy on subclinical atherosclerosis, serum levels of CD40 ligand, serum amyloid A and monocyte chemoattractant protein-1 **II)** limited evidence on the effects of periodontal therapy on arterial blood pressure, leucocyte counts, fibrinogen, tissue necrosis factor-α, sE-selectin, von Willebrand factors, d-dimers, matrix metalloproteinases, oxidative stress and CVD events, **III)** moderate evidence suggesting a negligible effect of periodontal therapy in reducing interleukin-6 and lipids levels, whilst a positive effect in reducing serum C-reactive protein levels and improving endothelial function.	Periodontal therapy triggers a short-term inflammatory response followed by (a) a progressive and consistent reduction of systemic inflammation and (b) an improvement in endothelial function. There is however limited evidence that these acute and chronic changes will either increase or reduce CVD burden of individuals suffering from periodontitis in the long term.	High (11)	All AMSTAR questions were satisfied