

Evidence Summary:

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DOI:

[10.1038/sj.bdj.2017.224](https://doi.org/10.1038/sj.bdj.2017.224)

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Document Version

Peer reviewed version

Citation for published version (Harvard):

Dietrich, T, Webb, I, Stenhouse, L, Pttani, A, Ready, D, Wanyonyi, K, White, S & Gallagher, JE 2017, 'Evidence Summary: The relationship between oral and cardiovascular disease', *British Dental Journal*, vol. 222, pp. 381-385. <https://doi.org/10.1038/sj.bdj.2017.224>

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Evidence Summary: The relationship between oral and cardiovascular disease

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Key Words:

Oral health, general health, stroke, tooth loss, caries, periodontal disease, oral health related quality of life, periodontal therapy, periodontal treatment, oral health promotion, surrogate markers, cardiovascular, cerebrovascular, atherosclerotic cardiovascular disease.

In brief

- There was a firm association between oral health (periodontitis, caries and tooth loss) and atherosclerotic cardiovascular disease (coronary heart disease, stroke, and peripheral vascular disease)
- There was no evidence 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 (eg endothelial function, inflammatory and oxidative stress markers)
- Oral health promotion improves oral health-related quality of life measures in stroke patients

Abstract

This paper reports on one review of four rapid reviews undertaken to explore the relationships between oral health and general medical conditions, in order to support teams within Public Health England, health practitioners and policy makers. This review aimed to explore the most contemporary evidence on whether poor oral health and cardiovascular disease occurs in the same individuals or populations, to outline the nature of the relationship between these two health outcomes and to discuss the implication of any findings for health services and future research. The review was undertaken by a group comprising consultant clinicians from medicine and dentistry, trainees, public health and academics. 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 relation 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), and accounted for up to 1-in-20 inpatient episodes. 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) (2). Data from NHS England spending for 2014 reveal that expenditure for CVD was in the region of £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 atherosclerotic cardiovascular 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.

Review methods

A rapid review of systematic reviews and/or meta-analyses published between 2005 and 2015 investigating the relationship between cardiovascular disease and oral health was performed. A rapid review involves 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, followed by 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.

Table 1

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.

Figure 2

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 agreed in group discussion.

Within the themes identified by this review, most of the papers examined the link between atherosclerotic and oral disease, of which 10 examined coronary heart disease and oral disease, and six cerebrovascular disease and oral disease. Of the 22 systematic reviews, 17 were found to be high quality based on AMSTAR tool (6-23), three were of moderate (24-26), and one (27), of low quality. For those with a score below 11, 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, together with the rationale, are presented for each paper in Table 1.

Results: evidence synthesis

The results are synthesised into six sections. Each section combines evidence related to the relationship between a cardiovascular disease to an oral disease or impact of oral disease management.

1] 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 patients with periodontitis compared to those without.

III] Atherosclerotic 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) Cerebrovascular disease stroke 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) reported that 12 out of 15 studies showed an increased risk of *all-cause mortality* among individuals with high numbers of missing teeth; seven out of nine 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.

III] 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.

IV] 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 of moderate quality evaluated the potential association between apical periodontitis/endodontic disease and CVD, but found scarce evidence to support this link (27).

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

VJ Stroke and oral health promotion

Two systematic reviews (9, 26), 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 a stroke, oral health promotion can have a significant impact on their oral health.

VIJ 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), and reduction in carotid intima-medial thickness (c-IMT) (23). D'Aiuto et al. (2013) reported moderate evidence of a negligible effect of periodontal therapy in reducing interleukin-6 and lipid levels, 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 metalloproteinase, 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 chemo attractant 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.

Summary

There is high quality evidence to support an association between cardiovascular disease and oral health. This evidence mainly is related to the association between chronic periodontitis and atherosclerotic heart disease and is independent of confounding factors as drawn from epidemiological observational studies. Notably, no causal relationship has been established between cardiovascular disease and periodontal disease and (6), and the results suggest associations of varied strength between other oral diseases such as 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. Kelly et al in 2013 had similarly highlighted significant structural and methodological variability among the published systematic reviews and meta-analyses regarding

the connection between periodontitis and CHD (28). A strength of this review is the high number of meta-analyses. Furthermore, the focus on a wide range of cardiovascular and oral disease provides a wider range of evidence identifying areas of interest that may require further research.

The findings in this review have significant implications for health services and research. In relation to health services generally, healthcare professionals diagnosing and managing oral and cardiovascular disease should be aware of the associations highlighted in this review and the implications for patient care and health outcomes. A concerted effort is necessary across disciplines to ensure relevant cross-referrals and risk assessments in order to reduce the incidence and improve prognosis of these diseases.

Dental professionals 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. For example, the NHS Health Check has been introduced for people aged 40-74 to focus on the principle behavioural and physiological risk factors for CVD. Dental professionals should encourage uptake of this service for those considered at increased risk of CVD.

Quality of life of patients who have suffered stroke is significantly altered and the implication of changes in dexterity and oral muscular function can cause further challenges. A daily regime of care should be instituted to maintain oral health and activities to support carers in this role will also be helpful (11).

There is room for well-designed longitudinal studies which can further examine the associations between these two diseases and surrogate markers of disease. It is only following this that firm recommendations can 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.

Table 2

In summary, there is a firm association between oral health (periodontitis, caries and tooth loss) and atherosclerotic cardiovascular disease; that is coronary heart disease, stroke, peripheral vascular disease. There is little or no evidence to support any links between oral health and other forms of cardiovascular disease that is 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, improve oral health-related quality of life measures in stroke patients.

Acknowledgements

We would like to acknowledge the support of Dr Francesco D’Aiuto of University College London on this paper and during workshops. We would like to acknowledge the support of Public Health England, the Royal College of Surgeons and the British Dental Association.

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. London: British Heart Foundation, 2015.
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 Dec;83(12):1449-54. PubMed PMID: 22420873. Epub 2012/03/17. eng.
5. Steele J, O'Sullivan I. Adult Dental Health Survey 2011 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*. 2015;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. 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.
27. Cotti E, Dessi C, Piras A, Mercurio 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.
28. 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.