Cochrane
Library

Cochrane Database of Systematic Reviews

Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis (Review)

Li C, Lv Z, Shi Z, Zhu Y, Wu Y, Li L, Iheozor-Ejiofor Z

Li C, Lv Z, Shi Z, Zhu Y, Wu Y, Li L, Iheozor-Ejiofor Z.

Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis.

Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD009197.

DOI: 10.1002/14651858.CD009197.pub3.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	5
OBJECTIVES	6
METHODS	6
RESULTS	10
Figure 1.	11
Figure 2.	13
DISCUSSION	14
AUTHORS' CONCLUSIONS	15
ACKNOWLEDGEMENTS	16
REFERENCES	16
CHARACTERISTICS OF STUDIES	22
DATA AND ANALYSES	33
Analysis 1.1. Comparison 1 Secondary prevention: periodontal treatment versus community care, Outcome 1 All cardiovascular events (25 months).	33
Analysis 1.2. Comparison 1 Secondary prevention: periodontal treatment versus community care, Outcome 2 Serum hs-CRP (1 year).	34
Analysis 1.3. Comparison 1 Secondary prevention: periodontal treatment versus community care, Outcome 3 Number of participants who had high hs-CRP (1 year).	34
Analysis 1.4. Comparison 1 Secondary prevention: periodontal treatment versus community care, Outcome 4 Adverse events related to the treatment (25 months).	35
ADDITIONAL TABLES	35
APPENDICES	37
WHAT'S NEW	43
CONTRIBUTIONS OF AUTHORS	44
DECLARATIONS OF INTEREST	44
SOURCES OF SUPPORT	44
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	45
INDEX TERMS	45

Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis

Chunjie Li¹, Zongkai Lv², Zongdao Shi³, Ye Zhu⁴, Yafei Wu⁵, Longjiang Li⁶, Zipporah Iheozor-Ejiofor⁷

¹Department of Head and Neck Oncology, State Key Laboratory of Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu, China. ²Department of Stomatology, Nan Chong Central Hospital, Second Clinical Medical College of Chuan Bei Medical College, Nanchong, China. ³Department of Oral and Maxillofacial Surgery, West China Hospital of Stomatology, Sichuan University, State Key Laboratory of Oral Diseases, Chengdu, China. ⁴Department of Cardiovascular Disease, West China Hospital, Sichuan University, Chengdu, China. ⁵Department of Periodontology, West China Hospital of Stomatology, Sichuan University, State Key Laboratory of Oral Diseases, Chengdu, China. ⁶Department of Head and Neck Oncology, West China Hospital of Stomatology, Sichuan University, State Key Laboratory of Oral Diseases, Chengdu, China. ⁷Division of Nursing, Midwifery and Social Work, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

Contact address: Chunjie Li, Department of Head and Neck Oncology, State Key Laboratory of Oral Diseases, West China Hospital of Stomatology, Sichuan University, No. 14, Section Three, Ren Min Nan Road, Chengdu, Sichuan, 610041, China. lichunjie@scu.edu.cn, lichunjie07@qq.com.

Editorial group: Cochrane Oral Health Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 11, 2017.

Citation: Li C, Lv Z, Shi Z, Zhu Y, Wu Y, Li L, Iheozor-Ejiofor Z. Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No.: CD009197. DOI: 10.1002/14651858.CD009197.pub3.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

There is an association between chronic periodontitis and cardiovascular disease (CVD). However, it is not known whether periodontal therapy could prevent or manage CVD in patients with chronic periodontitis.

Objectives

The objective of this systematic review was to investigate the effects of periodontal therapy in preventing the occurrence of, and management or recurrence of, CVD in patients with chronic periodontitis.

Search methods

Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 31 August 2017), the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2017, Issue 7), MEDLINE Ovid (1946 to 31 August 2017), Embase Ovid (1980 to 31 August 2017) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL EBSCO) (1937 to 31 August 2017). The US National Institutes of Health Trials Registry (ClinicalTrials.gov), the [World Health Organization International Clinical Trials Registry Platform](http://www.worldhealthorganization.international-clinical-trials-registry-platform) and Open Grey were searched for ongoing trials. No restrictions were placed on the language or date of publication when searching the electronic databases.

We also searched the Chinese BioMedical Literature Database (1978 to 27 August 2017), the China National Knowledge Infrastructure (1994 to 27 August 2017), the VIP database (1989 to 27 August 2017) and Sciencepaper Online (2003 to 27 August 2017).

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs were considered eligible. Studies were selected if they included patients with a diagnosis of chronic periodontitis and previous CVD (secondary prevention studies) or no CVD (primary prevention studies); patients in the intervention group received active periodontal therapy compared to maintenance therapy, no periodontal treatment or another kind of periodontal treatment in the control group.

Data collection and analysis

Two review authors carried out the study identification, data extraction and risk of bias assessment independently and in duplicate. Any discrepancies between the two authors were resolved by discussion or with a third review author. A formal pilot-tested data extraction form was adopted for the data extraction, and the Cochrane tool for risk of bias assessment was used for the critical appraisal of the literature.

Main results

No studies were identified that assessed primary prevention of CVD in people with periodontitis. One study involving 303 participants with $\geq 50\%$ blockage of one coronary artery or a coronary event within three years, but not the three months prior, was included. The study was at high risk of bias due to deviation from the protocol treatment allocation and lack of follow-up data. The trial compared scaling and root planing (SRP) with community care for a follow-up period of six to 25 months. No data on deaths (all-cause or CVD-related) were reported. There was 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). 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 166.82) were also not statistically significant. The study did not assess modifiable cardiovascular risk factors, other blood test results, heart function parameters or revascularisation procedures.

Authors' conclusions

We found very low quality evidence that was insufficient to support or refute whether periodontal therapy can prevent the recurrence of CVD in the long term in patients with chronic periodontitis. No evidence on primary prevention was found.

PLAIN LANGUAGE SUMMARY

Treatment for gum disease (periodontitis) for the management of disease involving the heart and blood vessels in patients with chronic gum disease

Review question

The main question addressed by this review produced by Cochrane Oral Health was whether or not treatment for moderate to severe gum disease (periodontitis) also has an effect on the prevention or management of heart and blood vessel (cardiovascular) disease.

Background

Gum disease (periodontitis) is a common chronic or persisting condition that can get worse over time. It involves inflammation of the gums, which surround and support the teeth, causing swollen and painful gums and in severe cases loss of the bone (alveolar) that supports the teeth.

Clinical investigations have shown that there might be a link or association between chronic, ongoing gum disease (periodontitis) and heart and blood vessel disease (cardiovascular disease). Some investigators believe that the treatment for gum disease, which gets rid of bacteria and infection and controls inflammation, might prevent the occurrence or recurrence of heart disease.

Study characteristics

The evidence on which this review is based is from searches up to 27 August 2017. The included randomised controlled study involved 303 participants.

Key results

At present there is only one suitable study looking at this issue. The study had problems with its design. Based on this evidence it was not possible to determine whether or not treatment for gum (periodontal) disease has any effect on the occurrence or recurrence of heart disease in people with chronic gum disease.

Quality of the evidence

The quality of the evidence was very low as there was only one study with problems in its design and how the study was conducted.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

Secondary prevention: periodontal treatment versus community care for the management of cardiovascular disease in patients with chronic periodontitis						
Patient or population: patients with cardiovascular disease and chronic periodontitis Settings: the USA Intervention: secondary prevention, periodontal treatment versus community care						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Secondary prevention: periodontal treatment versus community care				
All-cause and CVD-related death			Outcomes not reported			
All cardiovascular events Follow-up: 25 months	Study population (control group incidence)		RR 0.72 (0.23 to 2.22)	303 (1 study)	⊕○○○ very low ^{1,2}	
	46 per 1000	33 per 1000 (11 to 102)				
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in the table. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: confidence interval; CVD: cardiovascular disease; RR: risk ratio</p>						
GRADE Working Group grades of evidence						
High quality: Further research is very unlikely to change our confidence in the estimate of effect.						
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.						
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.						
Very low quality: We are very uncertain about the estimate.						

¹ Lack of blinding. Poor compliance with study protocol

² Wide confidence interval

BACKGROUND

Description of the condition

Cardiovascular disease (CVD) covers a wide array of disorders (including diseases of the cardiac muscle and the vascular system supplying the heart, brain and other vital organs) such as coronary heart disease (with narrowing or blockage of the coronary arteries, which can cause angina and myocardial infarction) and stroke (with narrowing, blockage or haemorrhage of the cerebrovascular system), which are the world's largest killers causing the death of 17.1 million individuals per year (Nabel 2003; Jamison 2006). There are a variety of risk factors involved in the pathogenesis of CVD, such as smoking or passive smoking (Law 1997; He 1999; Kallio 2010), hypertension, excess sodium intake (Strazzullo 2009) and hyperlipidaemia (Austin 1999). Numerous successful modalities of treatment that are based on these aetiological or risk factors have been developed (Brunner 2007; Law 2009; Manktelow 2009). However, in modern society people are increasingly exposed to such factors and the aforementioned therapies are still not enough, thus the incidence of CVD increases year on year (WHO 2007).

Recently considerable attention has been paid to the aetiological role of acute or chronic infections on CVD, and infections which accelerate vascular inflammation and promote thrombosis of vascular vessels (Herzberg 2005; Viles-Gonzalez 2006) are believed to be a secondary pathogenic pathway (Smeeth 2004; Hansson 2006; Moutsopoulos 2006). Among the infections, periodontitis might be the most common. It is an infectious disease resulting in inflammation within the supporting tissues of teeth resulting in progressive attachment and alveolar bone loss (Armitage 1999). In the last century, periodontitis was reported to affect 6% to 20% of the population (Oliver 1991; AAP 1999); and the estimate of disease in the United States (US) population exceeds 47%. In those over 65 years, 64% have either moderate or severe periodontitis based on a recently published article (Eke 2012). There are two reasons why periodontitis and CVD are believed to be related. Firstly, the levels of systemic inflammation increase when moderate or severe periodontitis is present, and when treating periodontitis there is a clear reduction in the clinical signs with a decrease in the levels of systemic inflammatory mediators (Tonetti 2007; Paraskevas 2008). Secondly, the periodontal bacteria may invade the damaged periodontal tissue, enter the bloodstream and further invade the cardiovascular system. Several periodontal pathogens, such as *P. gingivalis*, *B. forsythus*, *P. intermedia* and *A. actinomycetemcomitans* (Haraszthy 2000; Padilla 2006) have been detected in carotid atheromas by polymerase chain reaction. Experimental studies have shown that the presence of these periodontal pathogens and oral bacteria in the atheromas could induce platelet activation and aggregation through collagen-like platelet aggregation-associated protein expression. The activated and aggregated platelets could then play an important role in

atheromatous formation and thrombosis, and finally lead to cardiovascular events (Herzberg 1983; Herzberg 1996). Besides this, periodontal bacteria may play a role in the formation of coronary atherosclerotic plaques, which is indirectly proven by the presence of bacterial DNA from the oral pathogenic micro-organisms in coronary atherosclerotic plaques and the special characteristics of the aortic aneurysms in cardiovascular disease patients harbouring *P. gingivalis* (Mahendra 2010; Nakano 2011). They can induce cell-specific innate immune inflammatory pathways causing and maintaining a chronic state of inflammation at sites distant from the periodontitis (Hayashi 2010). Also, an indirect association between the two diseases was identified by investigators as they share similar risk factors such as smoking, diabetes mellitus, obesity and hypertension (Friedewald 2009; Han 2017). The association between periodontitis and CVD was proved by some clinical trials and further confirmed by meta-analysis (Janket 2003; Scannapieco 2003; Khader 2004). Based on this evidence, some investigators have concluded that there could be a mild to moderate association between periodontitis and CVD (Genco 2002; Hujoel 2002; Hansen 2016).

As a relationship between periodontitis and CVD is evident, it is rational to explore whether CVD can be managed or its occurrence or recurrence prevented by treating periodontitis.

Description of the intervention

It is believed that bacterial infection is the main aetiological factor for periodontitis. Other factors such as occlusal trauma, calculus and smoking would be considered as risk factors accelerating the progression of periodontitis (Meng 2009). Fortunately, there are several effective ways to control these factors and further control periodontitis. Full mouth disinfection, supragingival and subgingival scaling and root planing (SRP) could remove the periodontal bacteria or calculus and create a relatively healthy environment to reduce bacterial regrowth (Eberhard 2008; Worthington 2013). Occlusal adjustment has also been reported as an effective method by eliminating the harmful occlusal trauma which induces abnormal stress on the periodontal tissue (Weston 2008). Periodontal surgery, including guided tissue regeneration (GTR), replaces the lost or necrotic bone and periodontal tissue (Needleman 2006; Esposito 2009). All of these therapies play a role in reducing the biofilm or number of bacteria and controlling the accelerating factors. Such maintenance and preventive interventions should be adopted for periodontitis sufferers as a life-long commitment to control periodontal inflammation and disease recurrence. Periodontal medicine has recently been created and is now recognised. It aims to treat the systemic diseases which are suspected to be associated with periodontal disease through applying periodontal therapies. Up to now, one Cochrane systematic review has shown that periodontal treatment could help to control diabetes mellitus (Simpson 2015), and another found low-quality evidence that periodontal treatment may reduce low birth weight

(less than 2500g) (Iheozor-Ejiofor 2017). One ongoing Cochrane systematic review is focusing on periodontal therapies in the care of people with rheumatoid arthritis (Vergnes 2012). It is recognised that such treatments may have a beneficial effect not only on the periodontal disease but also on some major systemic diseases.

How the intervention might work

Periodontal treatment could clean up the infectious sources and control the acceleration of periodontitis. Some studies have already confirmed that high blood pressure could be lowered and serum inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) could be significantly reduced after such treatment (D'Aiuto 2005; Blum 2007; Martín-Cabezas 2016). Tüter and co-workers indicated that periodontal treatment with a subantimicrobial dose of doxycycline could increase serum levels of apolipoprotein-A and high-density lipoprotein, reduce total cholesterol levels and further decrease the risk of cardiovascular events (D'Aiuto 2005; Tüter 2007). However, as we have mentioned previously, periodontitis and CVD may have similar risk factors (smoking, obesity, hypertension and diabetes mellitus) some of which are modifiable and some non-modifiable. The mechanism of periodontal treatment in the management of CVD, which could be based on controlling periodontitis directly or changing the modifiable risk factors, or both, is still unknown.

Why it is important to do this review

Cochrane Oral Health undertook an extensive prioritisation exercise in 2014 to identify a core portfolio of titles that were the most clinically important ones to maintain on the Cochrane Library (Worthington 2015). This review was identified as a priority title by the periodontal expert panel (Cochrane Oral Health priority review portfolio).

Some studies have investigated the effects of periodontal treatment for the management of CVD, but the reliability of the methods and validity of their results should be further evaluated. This review aimed to evaluate the scientific quality of the studies, by the participants, specific interventions, comparisons and outcomes, and provide some evidence on the effect of periodontal therapy in CVD management for clinicians and consumers.

OBJECTIVES

The objective of this systematic review was to investigate the effects of periodontal therapy in preventing the occurrence of, and management or recurrence of, cardiovascular disease (CVD) in patients with chronic periodontitis.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials (RCTs) and quasi-RCTs with follow-up times $\geq$ one year that aimed to test the effects of different periodontal therapies for patients with cardiovascular disease (CVD) were eligible. The studies could be primary prevention studies or secondary prevention studies. In the former, the focus would be on using periodontal treatment to prevent the occurrence of CVD in patients who do not have CVD. Participants in the secondary prevention studies would presently have, or have previously been diagnosed with, CVD. Studies that did not focus on the primary or secondary prevention of CVD were excluded.

Types of participants

We considered for inclusion people meeting the following criteria, regardless of age, gender, race, social and economical status.

1. Diagnosis of at least moderate chronic periodontitis with pocketing greater than or equal to 4 mm.
2. Absence of any known genetic or congenital heart defects and aggressive periodontitis.
3. An existing or previous diagnosis of CVD (including angina, myocardial infarction, stroke); for primary prevention studies investigating the preventive effect of periodontal treatment on CVD participants should not have CVD.
4. Absence of other sources of inflammation such as pulpal infections and active caries.
5. No periodontal treatment within six months (participants should have active disease and not be in a periodontal maintenance programme).

We did not consider people with severe systemic diseases other than CVD, who were pregnant or lactating, or were unable to return for follow-up.

Types of interventions

- Active therapy: scaling and root planing (SRP), which included subgingival SRP or SRP in combination with systemic antibiotic or host modulation with or without other active remedies.
- Maintenance therapy (supragingival scaling, antimicrobial rinses) or no periodontal treatment with or without the same basic remedies as those in the intervention group.

Types of outcome measures

The outcomes were divided into two categories: primary outcomes (which would be the main outcomes considered when forming conclusions) and secondary outcomes (which would assist in forming conclusions from the primary outcomes). Any outcomes detected within less than one year of completion of the treatment were considered as short-term outcomes and were not reported while those detected at one year or more were reported as long-term outcomes.

Primary outcomes

1. All-cause and CVD-related death.
2. All cardiovascular events (angina, myocardial infarction, stroke).

Secondary outcomes

1. Modifiable cardiovascular risk factors: blood pressure; lipids including cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C).
2. Blood test results, including serum levels of high-sensitivity C-reactive protein (hs-CRP), apolipoprotein-A (APO-A), apolipoprotein-B (APO-B).
3. Heart function parameters (such as ejection fraction).
4. Revascularisation procedures.
5. Adverse events due to periodontal therapy (tooth sensitivity, mouth discomfort).

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions:

- Cochrane Oral Health's Trials Register (searched 31 August 2017) ([Appendix 1](#));
- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 7) in the Cochrane Library (searched 31 August 2017) ([Appendix 2](#));
- MEDLINE Ovid (1946 to 31 August 2017) ([Appendix 3](#));
- Embase Ovid (1980 to 31 August 2017) ([Appendix 4](#)).
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 31 August 2017) ([Appendix 5](#));
- OpenGrey (searched 31 August 2017) ([Appendix 6](#)).

Subject strategies were modelled on the search strategy designed for MEDLINE Ovid. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy

designed by Cochrane for identifying randomised controlled trials and controlled clinical trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6 ([Lefebvre 2011](#)). We also searched the following databases:

- Chinese BioMedical Literature Database (CBM) (1978 to 27 August 2017);
- China National Knowledge Infrastructure (CNKI) (1994 to 27 August 2017);
- VIP (1989 to 27 August 2017).

The search attempted to identify all relevant studies irrespective of language. Non-English papers were translated.

Searching other resources

Cochrane Oral Health's Information Specialist searched the following databases for ongoing trials:

- US National Institutes of Health Trials Register (<http://clinicaltrials.gov>) (to 31 August 2017) ([Appendix 7](#));
- World Health Organization (WHO) Clinical Trials Registry Platform (<http://apps.who.int/trialsearch/default.aspx>) (to 31 August 2017) ([Appendix 8](#)).

We also searched Sciencepaper Online (2003 to 27 August 2017). The reference lists of all eligible trials were checked for additional studies. The first authors of all included studies were contacted by email for any ongoing or unpublished studies examining the efficacy and safety of periodontal therapy for the management of CVD.

Handsearching

All the Chinese professional journals and some important English journals in relation to the dental and cardiovascular fields were handsearched from the first issue to May 2011 (*see* [Additional Table 1](#) and [Additional Table 2](#) for details).

Data collection and analysis

Selection of studies

Two review authors (Chunjie Li and Zongkai Lv) carried out the study selection in duplicate according to the selection criteria. Titles and abstracts of the search results were initially screened to look for possible eligible studies. Full texts of these studies were retrieved and assessed by both review authors to further assess eligibility. Any disagreements on study inclusion were discussed to reach consensus and, when necessary, a third review author arbitrated. A PRISMA flow diagram of the whole process was used as recommended ([Liberati 2009](#)).

Data extraction and management

Two review authors (Chunjie Li and Zongkai Lv) carried out the data extraction in duplicate. Disagreements were resolved by discussion and an arbitrator was involved when the disagreement remained unresolved. A customised data extraction form designed in Microsoft Access 2007 was developed according to the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1.0 (Higgins 2011) and was pilot-tested using a sample of the studies focusing on this topic and was then applied to all the included studies. The following data were collected.

- Source: study identification (ID), reviewer ID, citation and contact details.
- Eligibility: reasons for inclusion and exclusion.
- Methods of the study: centres and their location, study duration, study design, sequence generation, allocation concealment, blinding and statistical methods.
- Participants: total number, setting, age and sex, diagnostic criteria for both cardiovascular disease and periodontitis, inclusion and exclusion criteria of the participants.
- Interventions: number of intervention groups; intervention details including periodontal therapy, control treatment and other active treatment; time, frequency, dose and usage of drugs administered.
- Outcomes: definition of outcome measures and units of the measurements, time points of measurement, sample size calculation, number of participants allocated to each group, numbers lost to follow-up and the reasons, detailed summary data for each group.
- Miscellaneous: funding, key conclusions of each article, correspondence required, and miscellaneous comments from review authors.

For studies which had multiple groups the data for all the groups, if they were relevant to this review, were to be extracted and displayed in the 'Characteristics of included studies' section of the systematic review.

If there was any missing information, the original investigators of the included studies were contacted for clarification.

Assessment of risk of bias in included studies

Risk of bias assessment was carried out following the approach described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1.0 (Higgins 2011) and the Cochrane systematic review by Shi 2013. Authors of the included studies were contacted by email to obtain or clarify any unreported or unclear information on the risk of bias of the studies. Two review authors (Chunjie Li and Zongkai Lv) independently measured the risk of bias according to the published article and the trial authors' responses. Any discrepancies were discussed and a third review author arbitrated when necessary.

Risk of bias assessment of the included studies

The risk of bias for each of the individual included studies was judged for seven domains (as identified in the Cochrane tool for risk of bias assessment). For each of the following domains a judgment of either 'low risk', 'high risk' or 'unclear risk' of bias was assigned.

1. Random sequence generation (selection bias): selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
2. Allocation concealment (selection bias): selection bias (biased allocation to interventions) due to inadequate concealment of the allocation.
3. Blinding of participants and personnel (performance bias): performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
4. Blinding of outcome assessment (detection bias): detection bias due to knowledge of the allocated interventions by outcome assessors.
5. Incomplete outcome data (attrition bias): attrition bias due to amount, nature or handling of incomplete outcome data.
6. Selective reporting (reporting bias): reporting bias due to selective outcome reporting.
7. Other bias: bias due to problems not covered elsewhere in the table, such as baseline imbalance, confounding bias, contamination and co-intervention, etc.

Summary risk of bias assessment at the study level

For some kinds of periodontal therapy it is nearly impossible to achieve participant blinding, so all the domains except the third were considered as key domains. Study limitations were allotted to one of the following three categories:

- low risk of bias, there was a low risk of bias for all key domains or any plausible bias was unlikely to seriously alter the study results;
- unclear risk of bias, there was an unclear risk of bias for one or more key domains or any plausible bias raised some doubt about the study results;
- high risk of bias, there was a high risk of bias for one or more key domains or any plausible bias might seriously weaken confidence in the results.

Measures of treatment effect

Selection of statistical methods was dependent on whether the data were dichotomous, continuous or presented as time-to-event. Both primary outcomes were treated as dichotomous data or time-to-event data.

For dichotomous data, risk ratios (RR) and 95% confidence intervals (CIs) were calculated. The Peto odds ratio (Peto OR) with 95% CI was used if the incidence of the events observed was low. For continuous data, mean differences (MD) and 95% CIs were calculated for change from baseline or the final values if they were

measured by similar indices. If the data were measured using different indices, standardised mean differences (SMD) and 95% CIs were to be adopted for the outcome measurements.

Unit of analysis issues

Cluster-randomised trials and studies with more than two intervention groups were to be analysed differently from RCTs. For cluster-randomised trials, to avoid any inappropriate analyses in the original studies, approximate analyses-effective sample sizes were to be adopted following the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1.0 (Higgins 2011). For studies with more than two intervention groups, as each meta-analysis addressed only a single pair-wise comparison two approaches were to be considered. The first was to combine groups to create a single pair-wise comparison and if this first approach failed the most relevant pair of interventions was to be selected.

Dealing with missing data

For trials with missing data, the review authors contacted the trial authors for supplementation of the data and clarification. If there was no reply, certain statistical methods were to be adopted. If the standard deviation (SD) of the continuous data was not reported, it was to be calculated through one of the following ways: (i) from the standard error (SE), 95% CIs, P values or t-values, ranges or interquartile ranges reported in the article; or (ii) if the SD of change from baseline values was missing it was to be calculated using the correlation coefficient. Intention-to-treat (ITT) analysis was conducted whenever possible. If the methods mentioned above could not be used, only the available data were to be analysed and interpreted with caution.

Assessment of heterogeneity

The χ^2 test for heterogeneity was to be implemented to examine if heterogeneity existed among the included studies. The I^2 statistic was to be applied to estimate the impact of the heterogeneity:

- 0% to 40% indicating slight heterogeneity;
- 30% to 60% indicating moderate heterogeneity;
- 50% to 90% indicating substantial heterogeneity;
- 75% to 100% indicating considerable heterogeneity.

Assessment of reporting biases

To avoid reporting biases, a comprehensive search that included grey literature and ongoing studies was carried out (see [Search methods for identification of studies](#)). Publication bias and other reporting biases were to be addressed with the help of the funnel plot only if there were more than 10 trials providing results in one outcome. The asymmetry of the funnel plot would reveal a potential publication bias and be further tested by the methods

introduced by Egger 1997 (continuous outcomes) and Rücker 2008 (dichotomous outcomes).

Data synthesis

Data would be pooled if there was more than one study with similar comparisons that reported the same variable. Fixed-effect or random-effects models were to be adopted depending on the number of studies included in the meta-analysis: a random-effects model would be used if there were four studies or more, otherwise a fixed-effect model would be adopted.

The method of the meta-analysis for computing different kinds of data varied. The RevMan (Review Manager 2014) default fixed-effect model Mantel-Haenszel (M-H) method was used for dichotomous data; MD or SMD for continuous data, unless the data were only in the appropriate form for generic inverse variance (GIV) for continuous data; and for time-to-event data (O minus E and variance) the Peto or inverse variance (IV) method.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was to be conducted according to the different modes of periodontal treatment and different categories of CVD. If there was clinical heterogeneity, subgroup analysis was also to be implemented however this was not possible because of the low number of studies.

Sensitivity analysis

To test the stability of the conclusions, sensitivity analysis was to be carried out based on different assumptions such as excluding studies with evident biases, using different methods to deal with missing data, different models of meta-analysis, exclusion of studies causing significant statistical heterogeneity, ITT analysis. The results were to be reported in detail and their impact on the stability of the conclusions evaluated in the discussion section.

Presentation of main results

To provide key information on the effects and safety of periodontal therapy for CVD management in a quick and accessible format, a 'Summary of findings' table was presented. The summary of findings table shows the quality of a body of evidence on the primary outcomes (all-cause and CVD-related death, all cardiovascular events). Quality assessment of the body of evidence involved the consideration of risk of bias at the outcome level, directness of the evidence, heterogeneity, precision of effect estimates and risk of publication bias (see [Assessment of reporting biases](#)). The GRADE system for evaluating the quality of the evidence in systematic reviews (Atkins 2004; Guyatt 2008; Higgins 2011) was adopted by using the GRADEprofiler software, which was designed as an assessment of the quality of a body of evidence for each individual outcome. The quality was classified into four categories: high, moderate, low, and very low. The strength of the

recommendations derived from the evidence was to be considered as either strong or weak (Guyatt 2008).

RESULTS

Description of studies

For details of the studies examined and the reasons for inclusion or exclusion please *see* the [Characteristics of included studies](#), [Characteristics of ongoing studies](#), [Characteristics of studies awaiting classification](#) and [Characteristics of excluded studies](#) tables.

Results of the search

A total of 1261 records were identified from electronic search, including 1189 records identified from English language databases, 300 from Chinese databases; 7 records were retrieved from hand-searching. A total of 941 records were screened after duplicate removal. We rejected 889 of these. Full texts of the other 52 records were retrieved and we excluded 39 published studies (42 records) and three were ongoing studies. One study (three articles) is awaiting classification because its eligibility was not clear because all participants were female and had osteopenia of the lumbar spine or femoral neck. Some data needed confirmation from the authors. One study (four articles) was finally included.

The process of study identification is summarised in a flow diagram and presented in [Figure 1](#).

Figure 1. Study flow diagram.

Included studies

From the searches, only one randomised controlled trial (RCT) was identified (303 participants).

1. Primary prevention

No study addressing primary prevention was identified.

2. Secondary prevention

The only included study was a secondary prevention study ([PAVE 2008](#)). It is a multicentre, parallel group, single-blind RCT with 303 participants randomised into the periodontal treatment group or the community care group.

Participants

Participants had to have $\geq 50\%$ blockage of one coronary artery or have had a coronary event within three years but $\geq$ three months previously. The periodontal inclusion criteria were: the presence of at least six natural teeth, including third molars, with at least three teeth with probing pocket depth (PPD) ≥ 4 mm, at least two teeth with interproximal clinical attachment loss (CAL) ≥ 2 mm, and $\geq 10\%$ of sites having bleeding on probing (BOP).

Intervention

The intervention group ($n = 151$) received oral hygiene instruction and one regimen of full mouth scaling and root planing (SRP) with local anaesthesia (30% of the treatment being completed $>$ two months after randomisation). Only 92.7% of the participants received the treatment; and one participant received SRP outside the study.

Control

Participants in the control group (community care group) ($n = 152$) received oral hygiene instruction and were given a copy of their oral radiographs, a letter stating the tentative oral findings, and were recommended to seek the opinion of a dentist (9% of the participants in the control group got SRP outside the study within six months and 11% of them got SRP within the entire follow-up period).

Outcome

The participants were observed for 6 months to 25 months. The following outcomes were reported: serious cardiovascular adverse events (all cardiovascular events), serum hs-CRP, number of participants that had high hs-CRP, and adverse events measured as the development of an undesirable medical or dental condition or the deterioration of a pre-existing medical or dental condition following or during exposure to a pharmaceutical product or medical or dental procedure, whether or not considered causally related to the intervention. Only data on adverse events due to periodontal therapy were analysed in this review.

Excluded studies

Thirty-eight studies (41 articles) were excluded based on the inclusion and exclusion criteria. The reasons for exclusion are listed in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

The only included study was at high risk of bias. See the [Characteristics of included studies](#) table and [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Random sequence generation: a computer generated randomised table was used and was considered adequate.
Allocation concealment: central allocation was adopted, which was graded as adequate.

Blinding

Blinding of participants and personnel: due to the nature of the intervention (periodontal treatment), it was impossible to achieve the blinding of participants and personnel.
Blinding of outcome assessment: blinding of outcome assessment was reported.

Incomplete outcome data

There were 21 (6.9%) participants lost to follow-up by the six-month clinic visit. In one year only 37 of the 303 participants received follow-up. The number of participants lost to follow-up by study group was not specifically reported, therefore it was not clear whether there was a difference between the groups in that regard. Follow-up data at other time points were not reported.

Selective reporting

All the variables were reported as stated in the protocol so the study was considered to be at low risk of reporting bias.

Other potential sources of bias

About 92.7% of the participants in the treatment group received the treatment. One participant in the intervention group received SRP outside the study while 11% of the participants in the control group had received SRP by the end of the follow-up period. Contamination and co-intervention resulted in a high risk of other biases.

Effects of interventions

See: [Summary of findings for the main comparison Secondary prevention: periodontal treatment versus community care for the management of cardiovascular disease in patients with chronic periodontitis](#)

1. Primary prevention

There was no relevant study on primary prevention.

2. Secondary prevention

2.1 Periodontal treatment versus community care

Participants in the periodontal treatment group, who received scaling and root planing (SRP) and advice, were compared with those in the community care group, who only received advice.

2.1.1 All-cause death

Not reported.

2.1.2 All CVD-related death

Not reported.

2.1.3 All cardiovascular events

Of the 15 serious adverse events (SAE) reported, 12 were cardiovascular events. In the article the authors did not clearly report the number of non-cardiovascular events in each group, but they stated via e-mail correspondence that all the three non-cardiovascular SAEs were in the community care group. Five participants in the periodontal treatment group reported cardiovascular events during the 25 months of the study compared to seven participants in the community care group. There was no significant difference in cardiovascular events when patients who received periodontal treatment were compared to those who received community care (risk ratio (RR) 0.72; 95% confidence interval (CI) 0.23 to 2.22) ([Analysis 1.1](#)).

2.1.4 Blood test results

Serum high-sensitivity C-reactive protein (hs-CRP) was tested at one year but the results showed that SRP had no significant effect on serum hs-CRP compared to community care (mean difference (MD) 0.62; 95% CI -1.45 to 2.69) ([Analysis 1.2](#)).

The number of participants who had high CRP was also analysed. High CRP, defined as CRP > 3 mg/l, was reported at one year follow-up but the results were not statistically significant (RR 0.77; 95% CI 0.32 to 1.85) ([Analysis 1.3](#)).

2.1.5 Adverse events due to periodontal therapy

During the 25 months, four adverse events (high blood pressure, a tooth abscess, elevated blood pressure, and a bicycle accident) occurred in the treatment group (RR 9.06; 95% CI 0.49 to 166.82). The effect was not statistically significant ([Analysis 1.4](#)).

DISCUSSION

Summary of main results

The aim of the review was to evaluate the effect of periodontal treatment in the primary and secondary prevention of cardiovascular disease (CVD) in patients with chronic periodontitis. Through a comprehensive search we identified 933 records of which only one randomised controlled trial (RCT) (303 participants) qualified for inclusion. The RCT focused on the effect of periodontal treatment for the secondary prevention of CVD in patients with chronic periodontitis. No primary prevention studies were identified, but some were excluded because of a short follow-up period. For secondary prevention, periodontal treatment was compared with community care. All-cause and CVD-related deaths were not reported in the trial. The study recorded 12 cardiovascular events but the results were not statistically significant. Also, serum high-sensitivity C-reactive protein (hs-CRP), the number of participants who had high CRP, and adverse events all reported non-significant results. Since there was only one study eligible for inclusion, which was also judged to be at high risk of bias, the results should be interpreted with caution.

Overall completeness and applicability of evidence

The review had aimed to include both primary and secondary prevention studies assessing periodontal treatment in CVD patients with chronic periodontitis. However, the only qualifying study was a secondary prevention study. The evidence from this review can be applied to adults in most age groups, except those over the

age of 75 years. The following outcomes are not covered in this review: modifiable cardiovascular risk factors, heart function parameters and revascularisation procedures. Although the investigators reported on adverse events and serious adverse events, there is no indication that death (all-cause or CVD-related) was an outcome objective of the trial. Therefore, this review does not provide any understanding about the effect of the intervention on deaths. Clinicians should also understand that we only assessed the effect of periodontal therapy for CVD management. Timing of periodontal therapy was not assessed. For patients with CVD, it is not safe to give active periodontal therapy to those had stroke within 6 months, or systolic blood pressure > 180 mmHg/diastolic blood pressure > 110 mmHg, or fasting blood pressure > 7.0 mmol/L/HbA1c > 7.5%, or platelet count < $60 \times 10^9/L$, or international normalized ratio ≥ 1.5 -2.0 (SP, CSA 2017; Renvert 2016). The results of this systematic review could not be applied to these patients.

Quality of the evidence

The evidence is very low quality due to serious limitations of the one identified study and the imprecision of the results (Summary of findings for the main comparison). The only included study was assessed as being at high risk of bias (Figure 2). This was because of the lack of blinding of patients and personnel and the failure of some patients to comply with their assigned therapy, thus confounding the results and reducing the observed treatment effect. Very serious imprecision in the result was due to the inclusion of only one study with an inadequate sample size. The authors indicated (via correspondence) that the outcome results covered a follow-up period of 0 to 25 months. Therefore, the results may have included both short- and long-term outcome results since the authors made no distinction in that regard.

Potential biases in the review process

The protocol for this review underwent some minor changes (Differences between protocol and review). Some of the changes include a change in the definition of chronic periodontitis to include patients with a pocket depth of 4 mm or more. The follow-up period was also changed to $\geq$ one year and heart function parameters were included in the protocol as a secondary outcome. These changes may be justified but could still be a source of bias in the review process.

Treatment for CVD might influence periodontal health. Current research has indicated the anti-microbial effect of statins to *P. gingivalis* and *A. actinomycetemcomitans* (Emani 2014). Magán-Fernández 2014 concluded that intake of simvastatin is associated with increasing serum osteoprotegerin concentrations, and this could have a protective effect against bone breakdown and periodontal attachment loss. During the trial, investigators

could not control the use of CVD drugs, which could influence final periodontal health in every group and cause contamination.

Agreements and disagreements with other studies or reviews

Other reviews focusing on the preventive or treatment effects of periodontal therapy and oral health promotion for the management of cardiovascular diseases have been published (Ioannidou 2006; Lam 2010) and they show inconsistent results with respect to the effect of periodontal therapy on systemic markers. Whilst the results of our review may be in agreement with the Ioannidou 2006 review, which found no significant difference in serum hs-CRP levels in patients with severe periodontal disease that underwent non-surgical periodontal treatment. The two reviews are largely incomparable with this present review because of the inadequate follow-up period.

AUTHORS' CONCLUSIONS

Implications for practice

We found very low quality evidence that was insufficient to determine the effect of periodontal treatment on cardiovascular disease (CVD) in patients with chronic periodontitis. Therefore, we are unable to make conclusions regarding the effect of periodontal treatment on cardiovascular events, serum high-sensitivity C-reactive protein (hs-CRP), the number of patients with high CRP and adverse events. This review did not find any trials examining the primary preventive effect of periodontal treatment on CVD in patients with chronic periodontitis.

Implications for research

Due to the insufficient number of trials, there is a need for more randomised controlled trials (RCTs) examining the secondary preventive effects of periodontal therapeutics. There is also a need for research on the primary preventive effects of periodontal treatment. Periodontal treatment can be a single- or multi-regimen of scaling and root planing (SRP). Since the included study only offered a single regimen, new studies could focus on the effect of multi-regimen SRP in controlling periodontitis. Multiple kinds of host modulation drugs could also be chosen.

There is need for more studies reporting on all-cause or cardiovascular-related deaths and cardiovascular events observed after long-term follow-up of one year or more. Most of the studies identified with our search strategy were excluded on the basis of inadequate follow-up period. The included study provided outcome data for a period covering 0 to 25 months, without indicating the time points when the outcome results were observed. Therefore, it is

important for new studies to have a long-term follow-up period whilst specifying the time when the outcome results were observed.

For future research, it is important to stratify study participants according to the severity of the periodontitis together with the number of remaining teeth. Again, certain confounding factors should be carefully considered and controlled for, such as acute inflammation, smoking and diabetes mellitus. Limitations of the included study were due to non-compliance with the protocol, incomplete follow-up and lack of blinding of participants and personnel. In future studies, lack of compliance with the study protocol and incomplete follow-up of the participants can be reduced, as suggested by [PAVE 2008](#), if patients are followed up by a cardiologist. Although blinding of the participants and personnel is difficult to achieve in most periodontal RCTs, blinded outcome assessment is still achievable. Offering supra-gingival scaling to the control group might be useful for blinding participants.

ACKNOWLEDGEMENTS

For this update, we acknowledge Professor Helen Worthington, Laura MacDonald and Anne Littlewood of Cochrane Oral Health.

For previous versions of this review, the review authors would like to thank:

- Cochrane Oral Health Information Specialist, Anne Littlewood, and Jane Ronson for designing the search strategies.

- Professor Helen Worthington (Co-ordinating Editor, Cochrane Oral Health), Luisa Fernandez Mauleffinch (Managing Editor) and Philip Riley (Methodologist), for their assistance in processing the systematic review.

- Professor Hongde Hu for helping with the title registration.

- Professor Jing Li from the Chinese Cochrane Center, Prof Philip J Wiffen, Dr Marialena Trivella and Dr Sally Hopewell from the UK Cochrane Centre, and Mrs Susan Furness from Cochrane Oral Health for their assistance and guidance in the conducting of the systematic review.

- Dr Yan Wang and Xiangyu Ma from West China College of Stomatology for their help with the revision of the systematic review.

- Dr Feng Li, Dr Qiushi Wang, Dr Chenyang Xiang, Dr Zhaoyang Ban and Dr Wenhong Dong for their help with handsearching.

- Professor Aubrey Sheiham for the Aubrey Sheiham Public Health & Primary Care Scholarship (2011) for supporting the systematic review.

- Dr Beck and Dr Couper ([PAVE 2008](#)) and Dr Ide ([Ide 2003](#)) who provided valuable information about the included study.

- We would also thank Professor Zongdao Shi for his special contribution to the first version of this systematic review.

REFERENCES

References to studies included in this review

PAVE 2008 {published and unpublished data}

- * Beck JD, Couper DJ, Falkner KL, Graham SP, Grossi SG, Gunsolley JC, et al. The Periodontitis and Vascular Events (PAVE) pilot study: adverse events. *Journal of Periodontology* 2008;**79**(1):90–6.
- Couper DJ, Beck JD, Falkner KL, Graham SP, Grossi SG, Gunsolley JC, et al. The Periodontitis and Vascular Events (PAVE) pilot study: recruitment, retention, and community care controls. *Journal of Periodontology* 2008;**79**(1):80–9.
- Offenbacher S, Beck JD, Moss K, Mendoza L, Paquette DW, Barrow DA, et al. Results from the Periodontitis and Vascular Events (PAVE) Study: a pilot multicentered, randomized, controlled trial to study effects of periodontal therapy in a secondary prevention model of cardiovascular disease. *Journal of Periodontology* 2009;**80**(2):190–201.
- van Dyke TE, Maupome G, Madden T, Grossi S, Gunsolley JC, Offenbacher S, et al. Periodontal Intervention for Cardiac Events: A Pilot Trial (Periodontitis and Cardiovascular Events or “PAVE”). www.ClinicalTrials.gov 2003. NCT00066053]

References to studies excluded from this review

Amar 2004 {unpublished data only}

- Amar S. Systemic Endothelial Consequences of Periodontal Disease (Impact of Gum Infection on Heart Disease). www.ClinicalTrials.gov 2004. NCT00093236]

Bokhari 2012 {published data only}

- Bokhari SA, Khan AA, Butt AK, Azhar M, Hanif M, Izhar M, et al. Non-surgical periodontal therapy reduces coronary heart disease risk markers: a randomized controlled trial. *Journal of Clinical Periodontology* 2012;**39**(11):1065–74.

Brown 2004 {published data only}

- Brown DL, Desai KK, Vakili BA, Nouneh C, Lee HM, Golub LM. Clinical and biochemical results of the metalloproteinase inhibition with subantimicrobial doses of doxycycline to prevent acute coronary syndromes (MIDAS) pilot trial. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2004;**24**(4):733–8.

Cullinan 2005 {unpublished data only}

- Cullinan M, Carle A. The Effect of a Triclosan Containing Dentifrice on the Relationship Between Periodontal

- Disease and Cardiovascular Disease (Cardiovascular and Periodontal Study: a Randomised Controlled Trial CAPS). www.anzctr.org.au 2005. ACTRN12605000593639]
- Cullinan 2015** *{published data only}*
Cullinan MP, Palmer JE, Carle AD, West MJ, Westerman B, Seymour GJ. The influence of a triclosan toothpaste on adverse events in patients with cardiovascular disease over 5-years. *Sci Total Environ* 2015;**508**:546–552.
- D'Aiuto 2005** *{published data only}*
* D'Aiuto F, Nibali L, Parkar M, Suvan J, Tonetti MS. Short-term effects of intensive periodontal therapy on serum inflammatory markers and cholesterol. *Journal of Dental Research* 2005;**84**(3):269–73.
D'Aiuto F, Parkar M, Nibali L, Suvan J, Lessem J, Tonetti MS. Periodontal infections cause changes in traditional and novel cardiovascular risk factors: results from a randomized controlled clinical trial. *American Heart Journal* 2006;**151**(5):977–84.
- Dietrich 2005** *{published data only}*
Dietrich T, García RI. Associations between periodontal disease and systemic disease: evaluating the strength of the evidence. *Journal of Periodontology* 2005;**76**(11 Suppl): 2175–84.
- Domínguez 2010** *{published data only}*
Domínguez A, Gómez C, García-Kass AI, García-Núñez JA. IL-1beta, TNF-alpha, total antioxidative status and microbiological findings in chronic periodontitis treated with fluorescence-controlled Er:YAG laser radiation. *Lasers in Surgery and Medicine* 2010;**42**(1):24–31.
- Ebersole 1997** *{published data only}*
Ebersole JL, Machen RL, Steffen MJ, Willmann DE. Systemic acute-phase reactants, C-reactive protein and haptoglobin, in adult periodontitis. *Clinical and Experimental Immunology* 1997;**107**(2):347–52.
- El-Sharkawy 2010** *{published data only}*
El-Sharkawy H, Aboelsaad N, Eliwa M, Darweesh M, Alshahat M, Kantarci A, et al. Adjunctive treatment of chronic periodontitis with daily dietary supplementation with omega-3 fatty acids and low-dose aspirin. *Journal of Periodontology* 2010;**81**(11):1635–43.
- Elter 2006** *{published data only}*
Elter JR, Hinderliter AL, Offenbacher S, Beck JD, Caughey M, Brodala N, et al. The effects of periodontal therapy on vascular endothelial function: a pilot trial. *American Heart Journal* 2006;**151**(1):47.
- Emingil 2011** *{published data only}*
Emingil G, Gürkan A, Atilla G, Kantarci A. Subantimicrobial-dose doxycycline and cytokine-chemokine levels in gingival crevicular fluid. *Journal of Periodontology* 2011;**82**(3):452–61.
- Fajardo 2010** *{published data only}*
Fajardo ME, Rocha ML, Sánchez-Marín FJ, Espinosa-Chávez EJ. Effect of atorvastatin on chronic periodontitis: a randomized pilot study. *Journal of Clinical Periodontology* 2010;**37**(11):1016–22.
- Golub 2002** *{published data only}*
Golub LM, Ryan ME, Lee H, Greenwald A, Sorsa T, Brown DL. Subantimicrobial doxycycline reduces biomarkers of systemic inflammation in heart disease and diabetes. *Journal of Periodontology* 2003;**74**:1405.
- Gottrehrer 2006** *{published data only}*
Gottrehrer NR, Berglund SE. Antimicrobial host response therapy in periodontics: a modern way to manage disease. *Dentistry Today* 2006;**25**(9):84–7.
- Gottrehrer 2007** *{published data only}*
Gottrehrer NR, Berglund SE. Antimicrobial host response therapy in periodontics: a modern way to manage disease, part 2. *Dentistry Today* 2007;**26**(1):74, 76, 78 passim.
- Gottrehrer 2007a** *{published data only}*
Gottrehrer NR, Martin JL. The standard of care for nonsurgical periodontal treatment for reducing the dental risk for cardiac disease. *Dentistry Today* 2007;**26**(11):100, 102, 104.
- Gunupati 2011** *{published data only}*
Gunupati S, Chava VK, Krishna BP. Effect of phase I periodontal therapy on anti-cardiolipin antibodies in patients with acute myocardial infarction associated with chronic periodontitis. *Journal of Periodontology* 2011;**82**(12):1657–64.
- Ide 2003** *{published and unpublished data}*
Ide M, McPartlin D, Coward PY, Crook M, Lumb P, Wilson RF. Effect of treatment of chronic periodontitis on levels of serum markers of acute-phase inflammatory and vascular responses. *Journal of Clinical Periodontology* 2003;**30**(4):334–40.
- Ide 2004** *{published data only}*
Ide M, Jagdev D, Coward PY, Crook M, Barclay GR, Wilson RF. The short-term effects of treatment of chronic periodontitis on circulating levels of endotoxin, C-reactive protein, tumor necrosis factor-alpha, and interleukin-6. *Journal of Periodontology* 2004;**75**(3):420–8.
- Kamil 2011** *{published data only}*
Kamil W, Al Habashneh R, Khader Y, Al Bayati L, Taani D. Effects of nonsurgical periodontal therapy on C-reactive protein and serum lipids in Jordanian adults with advanced periodontitis. *Journal of Periodontal Research* 2011;**46**: 616–21.
- Lösche 2007** *{published data only}*
Lösche W. Periodontitis and cardiovascular disease: periodontal treatment lowers plasma cholesterol. *Southern Medical Journal* 2007;**100**(7):663–4.
- Michalowicz 2009** *{published data only}*
Michalowicz BS, Novak MJ, Hodges JS, DiAngelis A, Buchanan W, Papapanou PN, et al. Serum inflammatory mediators in pregnancy: changes after periodontal treatment and association with pregnancy outcomes. *Journal of Periodontology* 2009;**80**(11):1731–41.
- Offenbacher 2006** *{published data only}*
Offenbacher S, Lin D, Strauss R, McKaig R, Irving J, Barros SP, et al. Effects of periodontal therapy during pregnancy

- on periodontal status, biologic parameters, and pregnancy outcomes: a pilot study. *Journal of Periodontology* 2006;**77**(12):2011–24.
- Ortiz 2009** {published data only}
Ortiz P, Bissada NF, Palomo L, Han YW, Al-Zahrani MS, Panneerselvam A, et al. Periodontal therapy reduces the severity of active rheumatoid arthritis in patients treated with or without tumor necrosis factor inhibitors. *Journal of Periodontology* 2009;**80**(4):535–40.
- Oz 2007** {published and unpublished data}
Oz SG, Fentoglu O, Kilicarslan A, Guven GS, Tanrtover MD, Aykac Y, et al. Beneficial effects of periodontal treatment on metabolic control of hypercholesterolemia. *Southern Medical Journal* 2007;**100**(7):686–91.
- Paju 2006** {published data only}
Paju S, Pussinen PJ, Sinisalo J, Mattila K, Doğan B, Ahlberg J, et al. Clarithromycin reduces recurrent cardiovascular events in subjects without periodontitis. *Atherosclerosis* 2006;**188**(2):412–9.
- Quintero 2010** {unpublished data only}
Quintero A, Valenzuela CY, Ibieta C, Jara L, Llancaqueo M, Lopez NJ. Effects of Periodontal Therapy on Markers of Systemic Inflammation in Subjects at Cardiovascular Disease Risk (Effects of Periodontal Therapy on Systemic Inflammation). www.ClinicalTrials.gov 2010. NCT01046435]
- Ramírez 2011** {published data only}
Contreras A, Ramírez JH. Impact of Periodontal Therapy on Endothelial Function (Periodontal Infection and Endothelial Dysfunction). www.ClinicalTrials.gov 2008. NCT00681564]
* Ramírez JH, Arce RM, Contreras A. Periodontal treatment effects on endothelial function and cardiovascular disease biomarkers in subjects with chronic periodontitis: protocol for a randomized clinical trial. *Trials* 2011;**12**:46. [DOI: doi:10.1186/1745-6215-12-46]
- Sun 2010** {published data only}
Sun WL, Chen LL, Zhang SZ, Ren YZ, Qin GM. Changes of adiponectin and inflammatory cytokines after periodontal intervention in type 2 diabetes patients with periodontitis. *Archives of Oral Biology* 2010;**55**(12):970–4.
- Taylor 2010** {published data only}
Taylor B, Tofter G, Morel-Kopp MC, Carey H, Carter T, Elliott M, et al. The effect of initial treatment of periodontitis on systemic markers of inflammation and cardiovascular risk: a randomized controlled trial. *European Journal of Oral Sciences* 2010;**118**(4):350–6.
- Tonetti 2007** {published data only}
Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, et al. Treatment of periodontitis and endothelial function. *New England Journal of Medicine* 2007;**356**(9): 911–20.
- Tüter 2007** {published data only}
Tüter G, Kurti B, Serdar M, Aykan T, Okyay K, Yücel A, et al. Effects of scaling and root planing and sub-antimicrobial dose doxycycline on oral and systemic biomarkers of disease in patients with both chronic periodontitis and coronary artery disease. *Journal of Clinical Periodontology* 2007;**34**(8): 673–81.
- Tüter 2010** {published data only}
Tüter G, Serdar M, Kurti B, Walker SG, Atak A, Toyman U, et al. Effects of scaling and root planing and subantimicrobial dose doxycycline on gingival crevicular fluid levels of matrix metalloproteinase-8, -13 and serum levels of HsCRP in patients with chronic periodontitis. *Journal of Periodontology* 2010;**81**(8):1132–9.
- Ushida 2008** {published data only}
Koshy G, Kawashima Y, Kiji M, Nitta H, Umeda M, Nagasawa T, et al. Effects of single-visit full-mouth ultrasonic debridement versus quadrant-wise ultrasonic debridement. *Journal of Clinical Periodontology* 2005;**32**(7): 734–43.
* Ushida Y, Koshy G, Kawashima Y, Kiji M, Umeda M, Nitta H, et al. Changes in serum interleukin-6, C-reactive protein and thrombomodulin levels under periodontal ultrasonic debridement. *Journal of Clinical Periodontology* 2008;**35**(11):969–75.
- Vidal 2009** {published data only}
Vidal F, Figueredo CM, Cordovil I, Fischer RG. Periodontal therapy reduces plasma levels of interleukin-6, C-reactive protein, and fibrinogen in patients with severe periodontitis and refractory arterial hypertension. *Journal of Periodontology* 2009;**80**(5):786–91.
- Wozakowska-Kapłoniak 2009** {published data only}
Wozakowska-Kapłoniak B, Filipiak KJ, Opolski G, Górski R. The importance of periodontal treatment in patients with cardiovascular diseases. *Kardiologia Polska* 2009;**67**(10): 1125–7.
- Yuan 2010** {published data only}
Yuan SZ, Hao M, Yang JL. The impact of periodontal treatment on serum hs-CRP of patient with both periodontitis and cardiovascular disease. *Chinese Journal of Integrative Medicine on Cardio-Cerebrovascular Disease* 2010;**8**(10):1176–8.
- Zhao 2010** {published data only}
Zhao H, Shu R. Association of full-mouth subgingival scaling and root planning and quadrant subgingival scaling and root planning with systemic acute inflammatory reaction. *Journal of Shanghai Jiaotong University (Medical Science)* 2010;**30**(11):1408–11.

References to studies awaiting assessment

- Payne 2011** {published data only}
* Payne JB, Golub LM, Stoner JA, Lee HM, Reinhardt RA, Sorsa T, et al. The effect of subantimicrobial-dose-doxycycline periodontal therapy on serum biomarkers of systemic inflammation: a randomized, double-masked, placebo-controlled clinical trial. *Journal of the American Dental Association* 2011;**142**(3):262–73.
Payne JB, Stoner JA, Nummikoski PV, Reinhardt RA, Goren AD, Wolff MS, et al. Subantimicrobial dose

doxycycline effects on alveolar bone loss in post-menopausal women. *Journal of Clinical Periodontology* 2007;**34**(9): 776–87.

Salminen A, Pussinen PJ, Payne JB, Stoner JA, Jauhiainen M, Golub LM, et al. Subantimicrobial-dose doxycycline treatment increases serum cholesterol efflux capacity from macrophages. *Inflammation Research* 2013;**62**(7):711–20.

References to ongoing studies

Azhar 2010 {unpublished data only}

Azhar M, Khan AA, Bokhari SAH. Influence of Periodontal Treatment on Systemic Inflammatory Mediators: hsC-reactive Protein, Fibrinogen and White Blood Cells in CHD Patients (Influence of Periodontal Treatment on Systemic Inflammatory Mediators Perio-CHD). www.ClinicalTrials.gov 2010. NCT01201746]

Haas 2013 {unpublished data only}

Haas AN. Periodontal Therapy in Coronary Artery Patients (PerioCardio). www.ClinicalTrials.gov 2013. NCT01609725]

Skilton 2011 {published data only}

Skilton MR, Maple-Brown LJ, Kapellas K, Celermajer DS, Bartold M, Brown A, et al. The effect of a periodontal intervention on cardiovascular risk markers in Indigenous Australians with periodontal disease: the PerioCardio study. *BMC Public Health* 2011;**11**:729.

Additional references

AAP 1999

American Academy of Periodontology. International workshop for classification of periodontal diseases and conditions. *Annals of Periodontology* 1999;**4**(1):7–112.

Armitage 1999

Armitage GC. Development of a classification system for periodontal diseases and conditions. *Annals of Periodontology* 1999;**4**(1):1–6.

Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.

Austin 1999

Austin MA. Epidemiology of hypertriglyceridemia and cardiovascular disease. *American Journal of Cardiology* 1999;**83**(9B):13F–16F.

Blum 2007

Blum A, Front E, Peleg A. Periodontal care may improve systemic inflammation. *Clinical and Investigative Medicine* 2007;**30**(3):E114–7.

Brunner 2007

Brunner EJ, Rees K, Ward K, Burke M, Thorogood M. Dietary advice for reducing cardiovascular risk. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD002128.pub3]

Eberhard 2008

Eberhard J, Jepsen S, Jervoe-Storm PM, Needleman I, Worthington HV. Full-mouth disinfection for the

treatment of adult chronic periodontitis. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: 10.1002/14651858.CD004622.pub2]

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.

Eke 2012

Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ, Beck J, et al. Prevalence of periodontitis in adults in the United States: 2009 and 2010. *Journal of Dental Research* 2012;**91**(10):914–20.

Emani 2014

Emani S, Gunjiganur GV, Mehta DS. Determination of the antibacterial activity of simvastatin against periodontal pathogens, Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans: An in vitro study. *Contemp Clin Dent* 2014;**5**(3):377–382.

Esposito 2009

Esposito M, Grusovin MG, Papanikolaou N, Coulthard P, Worthington HV. Enamel matrix derivative (Emdogain®) for periodontal tissue regeneration in intrabony defects. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD003875.pub3]

Friedewald 2009

Friedewald VE, Kornman KS, Beck JD, Genco R, Goldfine A, Libby P, et al. The American Journal of Cardiology and Journal of Periodontology editors' consensus: periodontitis and atherosclerotic cardiovascular disease. *Journal of Periodontology* 2009;**80**(7):1021–32.

Genco 2002

Genco R, Offenbacher S, Beck J. Periodontal disease and cardiovascular disease epidemiology and possible mechanisms. *Journal of the American Dental Association* 2002;**133** Suppl:14S–22S.

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924–6.

Han 2017

Han K, Park JB. Age threshold for moderate and severe periodontitis among Korean adults without diabetes mellitus, hypertension, metabolic syndrome, and/or obesity. *Medicine (Baltimore)* 2017;**96**(33):e7835.

Hansen 2016

Hansen GM, Egeberg A, Holmstrup P, Hansen PR. Relation of Periodontitis to Risk of Cardiovascular and All-Cause Mortality (from a Danish Nationwide Cohort Study). *Am J Cardiol* 2016;**118**(4):489–493.

Hansson 2006

Hansson GK, Robertson AK, Soderberg-Naucler C. Inflammation and atherosclerosis. *Annual Review of Pathology* 2006;**1**:297–329.

Haraszthy 2000

Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. *Journal of Periodontology* 2000;**71**(10):1554–60.

Hayashi 2010

Hayashi C, Gudino CV, Gibson FC 3rd, Genco CA. Review: Pathogen-induced inflammation at sites distant from oral infection: bacterial persistence and induction of cell-specific innate immune inflammatory pathways. *Molecular Oral Microbiology* 2010;**25**(5):305–16.

He 1999

He J, Vupputuri S, Allen K, Prerost MR, Hughes J, Whelton PK. Passive smoking and the risk of coronary heart disease—a meta-analysis of epidemiologic studies. *New England Journal of Medicine* 1999;**340**(12):920–6.

Herzberg 1983

Herzberg MC, Brintzenhofe KL, Clawson CC. Aggregation of human platelets and adhesion of *Streptococcus sanguis*. *Infection and Immunity* 1983;**39**(3):1457–69.

Herzberg 1996

Herzberg MC, Meyer MW. Effects of oral flora on platelets: possible consequences in cardiovascular disease. *Journal of Periodontology* 1996;**67 Suppl 10**:1138–42.

Herzberg 2005

Herzberg MC, Nobbs A, Tao L, Kilic A, Beckman E, Khammanivong A, et al. Oral streptococci and cardiovascular disease: searching for the platelet aggregation-associated protein gene and mechanisms of *Streptococcus sanguis*-induced thrombosis. *Journal of Periodontology* 2005;**76 Suppl 11**:2101–5.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hujoel 2002

Hujoel PP. Does chronic periodontitis cause coronary heart disease? A review of the literature. *Journal of the American Dental Association* 2002;**133 Suppl**:31S–36S.

Iheozor-Ejiofor 2017

Iheozor-Ejiofor Z, Middleton P, Esposito M, Glenny AM. Treating periodontal disease for preventing adverse birth outcomes in pregnant women. *Cochrane Database of Systematic Reviews* 2017, Issue 6. [DOI: 10.1002/14651858.CD005297.pub3]

Ioannidou 2006

Ioannidou E, Malekzadeh T, Dongari-Bagtzoglou A. Effect of periodontal treatment on serum C-reactive protein levels: a systematic review and meta-analysis. *Journal of Periodontology* 2006;**77**(10):1635–42.

Jamison 2006

Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al. *Disease Control Priorities in Developing*

Countries. 2nd Edition. Washington (DC): World Bank, 2006.

Janket 2003

Janket SJ, Baird AE, Chuang SK, Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 2003;**95**(5):559–69.

Kallio 2010

Kallio K, Jokinen E, Saarinen M, Hamalainen M, Volanen I, Kaitosaari T, et al. Arterial intima-media thickness, endothelial function, and apolipoproteins in adolescents frequently exposed to tobacco smoke. *Circulation. Cardiovascular Quality and Outcomes* 2010;**3**(2):196–203.

Khader 2004

Khader YS, Albashaireh ZS, Alomari MA. Periodontal diseases and the risk of coronary heart and cerebrovascular diseases: a meta-analysis. *Journal of Periodontology* 2004;**75**(8):1046–53.

Lam 2010

Lam OL, Zhang W, Samaranyake LP, Li LS, McGrath C. A systematic review of the effectiveness of oral health promotion activities among patients with cardiovascular disease. *International Journal of Cardiology* 2010;**151**(3):261–7.

Law 1997

Law MR, Morris JK, Wald NJ. Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. *BMJ* 1997;**315**(7114):973–80.

Law 2009

Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;**338**:b1665.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**(7):e1000100.

Magán-Fernández 2014

Magán-Fernández A, Papay-Ramírez L, Tomás J, Marfil-Álvarez R, Rizzo M, Bravo M, Mesa F. Association of simvastatin and hyperlipidemia with periodontal status and bone metabolism markers. *J Periodontol* 2014;**85**(10):1408–1415.

Mahendra 2010

Mahendra J, Mahendra L, Kurian VM, Jaishankar K, Mythilli R. 16S rRNA-based detection of oral pathogens in

- coronary atherosclerotic plaque. *Indian Journal of Dental Research* 2010;**21**(2):248–52.
- Manktelow 2009**
Manktelow BN, Potter JF. Interventions in the management of serum lipids for preventing stroke recurrence. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD002091.pub2]
- Martin-Cabezas 2016**
Martin-Cabezas R, Seelam N, Petit C, Agossa K, Gaertner S, Tenenbaum H, Davideau JL, Huck O. Association between periodontitis and arterial hypertension: A systematic review and meta-analysis. *Am Heart J* 2016;**180**:98–112.
- Meng 2009**
Meng HX. *Periodontology*. 5th Edition. Beijing: People's Medical Publishing House, 2009.
- Moutsopoulos 2006**
Moutsopoulos NM, Madianos PN. Low-grade inflammation in chronic infectious diseases: paradigm of periodontal infections. *Annals of the New York Academy of Sciences* 2006;**1088**:251–64.
- Nabel 2003**
Nabel EG. Cardiovascular disease. *New England Journal of Medicine* 2003;**349**(1):60–72.
- Nakano 2011**
Nakano K, Wada K, Nomura R, Nemoto H, Inaba H, Kojima A, et al. Characterization of aortic aneurysms in cardiovascular disease patients harboring *Porphyromonas gingivalis*. *Oral Disease* 2011;**17**(4):370–8.
- Needleman 2006**
Needleman IG, Worthington HV, Giedrys-Leeper E, Tucker RJ. Guided tissue regeneration for periodontal infra-bony defects. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD001724.pub2]
- Oliver 1991**
Oliver RC, Brown LJ, Loe H. Variations in the prevalence and extent of periodontitis. *Journal of the American Dental Association* 1991;**122**(6):43–8.
- Padilla 2006**
Padilla C, Lobos O, Hubert E, Gonzalez C, Matus S, Pereira M, et al. Periodontal pathogens in atheromatous plaques isolated from patients with chronic periodontitis. *Journal of Periodontal Research* 2006;**41**(4):350–3.
- Paraskevas 2008**
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.
- Renvert 2016**
Renvert S, Persson GR. Treatment of periodontal disease in older adults. *Periodontol* 2000 2016;**72**(1):108–119.
- Review Manager 2014 [Computer program]**
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
- Rücker 2008**
Rücker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analyses with binary outcomes. *Statistics in Medicine* 2008;**27**(5):746–63.
- Scannapieco 2003**
Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for nosocomial bacterial pneumonia and chronic obstructive pulmonary disease. A systematic review. *Annals of Periodontology* 2003;**8**(1): 54–69.
- Shi 2013**
Shi Z, Xie H, Wang P, Zhang Q, Wu Y, Chen E, et al. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. *Cochrane Database of Systematic Reviews* 2013, Issue 8. [DOI: 10.1002/14651858.CD008367.pub2]
- Simpson 2015**
Simpson TC, Weldon JC, Worthington HV, Needleman I, Wild SH, Moles DR, Stevenson B, Furness S, Theodor-Ejiofor Z. Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. *Cochrane Database of Systematic Reviews* 2015, Issue 11. [DOI: 10.1002/14651858.CD004714.pub3]
- Smeeth 2004**
Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *New England Journal of Medicine* 2004;**351**(25):2611–8.
- SP, CSA 2017**
Society of Periodontology, Chinese Stomatological Association. Consensus of Chinese experts on diagnosis of severe periodontitis and treatment principles of periodontitis in special population. *Zhonghua Kou Qiang Yi Xue Za Zhi* 2017;**52**(2):67–71.
- Strazzullo 2009**
Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ* 2009;**339**:b4567.
- Vergnes 2012**
Vergnes JN, Monsarrat P, Blaizot A, Nabet C, Cantagrel A, Sixou M, Furness S. Interventions for periodontal disease in people with rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD010040]
- Viles-Gonzalez 2006**
Viles-Gonzalez JF, Fuster V, Badimon JJ. Links between inflammation and thrombogenicity in atherosclerosis. *Current Molecular Medicine* 2006;**6**(5):489–99.
- Weston 2008**
Weston P, Yaziz YA, Moles DR, Needleman I. Occlusal interventions for periodontitis in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD004968.pub2]

WHO 2007

WHO. *Prevention of Cardiovascular Disease: Guidelines for Assessment and Management of Total Cardiovascular Risk*. Geneva: WHO Press, 2007.

Worthington 2013

Worthington HV, Clarkson JE, Bryan G, Beirne PV.
Routine scale and polish for periodontal health in adults.
Cochrane Database of Systematic Reviews 2013, Issue 11.
[DOI: 10.1002/14651858.CD004625.pub4]

Worthington 2015

Worthington H, Clarkson J, Weldon J. Priority oral
health research identification for clinical decision-making.
Evidence-based Dentistry 2015;**16**(3):69–71.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

PAVE 2008

Methods	<ul style="list-style-type: none"> • Type of study: parallel RCT • Stratification: randomisation was stratified by clinic and smoking status (whether subjects were smokers in the past 5 years) • Sample size calculation: not reported • Funding: NIDCR grant • Country: USA • Timeframe of the study: January 2003 to June 2005 <p>(other methods detail: please see the risk of bias table)</p>
Participants	<ul style="list-style-type: none"> • Centres: 5, the University at Buffalo, the University of North Carolina at Chapel Hill, Boston University, Kaiser Permanente Center for Health Research/Oregon Health and Sciences University, and the University of Maryland, Baltimore, Maryland • Inclusion criteria: to be eligible for the study, participants had to satisfy cardiac and periodontal inclusion criteria. For the cardiovascular criteria, participants had to be ≤ 75 years of age with $\geq 50\%$ blockage of one coronary artery or have had a coronary event within 3 years but ≥ 3 months previously, including myocardial infarction, coronary artery bypass graft surgery, or coronary transluminal angioplasty with or without a stent. The periodontal inclusion criteria were the presence of at least 6 natural teeth, including third molars, with at least 3 teeth with PPD ≥ 4 mm, at least 2 teeth with interproximal CAL ≥ 2 mm, and $\geq 10\%$ of sites having BOP. The criteria were applied after accounting for tooth extractions that were deemed clinically necessary • Exclusion criteria: not reported • Participants type: moderate to severe periodontitis and CVD • Number of participants: total 303; intervention group 151; control group 152 • Gender of participants: total, male 216, female 87; intervention group 104/47; control group 112/40 • Age of participants: total mean = 59.6 ± 8.8 (SD); intervention group 59.5 ± 9.1; control group 59.8 ± 8.7 • Lost to follow-up: by the time of the 6-month visit, 14 participants had withdrawn consent and 7 had been lost to follow-up. They were all considered as drop-outs. Among follow-up participants, only 228 had clinical follow-up. By the time of 1 year, only 37 had clinical follow-up
Interventions	<ul style="list-style-type: none"> • Both groups had hopeless teeth extracted before randomisation • Intervention group: oral hygiene instruction + full mouth SRP under local anaesthesia (30% of the treatment being completed > 2 months after randomisation; 92.7% of the participants received the treatment; 85% of them received supra-gingival scaling) • Control group (community care group): oral hygiene instruction and given a copy of their oral radiographs and a letter stating the tentative oral findings and recommended to seek the opinion of a dentist (9% of the participants in the control group got SRP outside the study within 6 months and 11% of them got SRP within the whole follow-up process) • Besides the study treatment, some participants sought dental care via other ways

	<p>(such as their own dental providers); 1% of the participants in the intervention group got SRP outside the study and 9% (6 months) and 11% (whole study follow-up) of the participants in the control group got SRP</p> <ul style="list-style-type: none"> • Duration of follow-up: 6 to 25 months
Outcomes	<ul style="list-style-type: none"> • Cardiovascular SAE (all cardiovascular events, measured during the whole study (means 25 months follow-up)) (the time frame was declared in the e-mail from the trial authors) • Serum hs-CRP (measured by latex-enhanced nephelometry at baseline, 6 months and 1 year) • Number of participants with high hs-CRP (serum hs-CRP > 3 mg/l measured at baseline, 6 months and 1 year) • AE (the development of an undesirable medical/dental condition or the deterioration of a pre-existing medical/dental condition following or during exposure to a pharmaceutical product or medical/dental procedure, whether or not considered causally related to the intervention, measured during the whole study) • SAE (an experience that is known with certainty or suspected with good reason to constitute a threat to life or to cause severe or permanent damage, measured during the whole study)
Notes	The author provided extra information about the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<ul style="list-style-type: none"> • Quote: "Randomization was stratified by clinic and smoking status (whether subjects were smokers in the past 5 years). A permuted block randomization scheme was used with a random mixture of block sizes within each stratum." In authors' letter "the randomization was by computer using a random number generator in SAS" • Comment: random number generation was adequate, low risk of bias
Allocation concealment (selection bias)	Low risk	<ul style="list-style-type: none"> • Quote: "Clinical centre staff obtained treatment assignments through a Web-based system designed and maintained by the coordinating centre. When a participant was deemed eligible, a staff member used the Web interface to enter the eligibility information, and the system returned the treatment assignment" • Comment: the allocation concealment was adequately achieved, low

		risk of bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	<ul style="list-style-type: none"> • Comment: it was not possible to achieve participant and personnel blinding in this study, high risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<ul style="list-style-type: none"> • Quote: in authors' letter "the outcome assessment was blinded" • Comment: the previous protocol stated that the study was a single-blind study, low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<ul style="list-style-type: none"> • Comment: in 6 months, 16/152 (10.5%) in the control group, 5/151 (3.3%) in the intervention group were lost to follow-up, and only 228/303 got clinical follow-up. In 1 year, only 37/303 got clinical follow-up. The follow-up status at other time points was unclear. It is not clear whether there was a significant difference between the study groups in losses to follow-up, unclear risk of bias
Selective reporting (reporting bias)	Low risk	<ul style="list-style-type: none"> • Comment: all the outcomes were reported, low risk of bias
Other bias	High risk	<ul style="list-style-type: none"> • Comment: only 92.7% of the participants in the intervention group received the treatment, 1% of the participants in intervention group got SRP outside the study and 9% (6 months) and 11% (whole study follow-up) of the participants in control group got SRP. Therefore this study had contamination and co-intervention, high risk of bias

AE = adverse events; BOP = bleeding on probing; CAL = clinical attachment level; CVD = cardiovascular disease; hs-CRP = high-sensitivity C-reactive protein; PPD = probing pocket depth; RCT = randomised controlled trial; SAE = serious adverse event; SD = standard deviation; SRP = scaling and root planing

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Amar 2004	Follow-up shorter than 1 year
Bokhari 2012	Follow-up shorter than 1 year
Brown 2004	No participants had periodontitis
Cullinan 2005	Participants in the intervention group did not get any active periodontal treatment
Cullinan 2015	Participants in the intervention group did not get any active periodontal treatment
D'Aiuto 2005	Follow-up shorter than 1 year
Dietrich 2005	A review article, not an RCT
Domínguez 2010	No cardiovascular patients involved, no CVD closely-related outcomes reported
Ebersole 1997	Not comparing periodontal treatment
El-Sharkawy 2010	No cardiovascular patients involved, no CVD closely-related outcomes reported
Elter 2006	Not an RCT
Emingil 2011	No cardiovascular patients involved, no CVD closely-related outcomes reported
Fajardo 2010	Participants got the same periodontal treatment in both groups
Golub 2002	No cardiovascular patients involved, no CVD closely-related outcomes reported
Gottehrer 2006	Not an RCT
Gottehrer 2007	Not an RCT
Gottehrer 2007a	Not an RCT
Gunupati 2011	Not an RCT
Ide 2003	Follow-up shorter than 1 year
Ide 2004	Not an RCT
Kamil 2011	Follow-up shorter than 1 year
Lösche 2007	A review article, not an RCT
Michalowicz 2009	All the participants were pregnant

(Continued)

Offenbacher 2006	All the participants were pregnant
Ortiz 2009	All the participants had rheumatoid arthritis
Oz 2007	Follow-up shorter than 1 year
Paju 2006	Participants in the intervention group did not get any active periodontal treatment
Quintero 2010	Participants included had obesity or diabetes or hypertension
Ramírez 2011	Follow-up shorter than 1 year
Sun 2010	All the participants had type 2 diabetes
Taylor 2010	Follow-up shorter than 1 year
Tonetti 2007	Follow-up shorter than 1 year
Tüter 2007	Follow-up shorter than 1 year
Tüter 2010	Follow-up shorter than 1 year
Ushida 2008	Follow-up shorter than 1 year
Vidal 2009	All the participants had refractory arterial hypertension
Wozakowska-Kapłon 2009	A review article, not an RCT
Yuan 2010	Not an RCT, it is a CCT
Zhao 2010	Half of the included participants had aggressive periodontitis

CCT = controlled clinical trial; CVD = cardiovascular disease; RCT = randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Methods	<ul style="list-style-type: none"> • Type of study: placebo-controlled, double-blinded parallel RCT • Stratification: the randomisation was stratified by study centre (University of Nebraska Medical Center College of Dentistry (UNMC COD) or Stony Brook) and current smoking status (current smoker or not current smoker) • Sample size calculation: reported • Funding: NIDCR grant • Country: USA • Timeframe of the study: June 2012 to October 2005
Participants	<ul style="list-style-type: none"> • Centres: 2, UNMC COD and the School of Dental Medicine at Stony Brook University (Stony Brook) • Inclusion criteria: 45-70 years of age at telephone screening; postmenopausal for at least 6 months and not receiving hormone replacement therapy (HRT); osteopenia of the lumbar spine or femoral neck (T-score of -1.0 to -2.5 inclusive); history of generalized moderate to advanced periodontitis and undergoing periodontal maintenance; and having at least 9 posterior teeth and at least 2 sites with probing depths ≥ 5 mm together with bleeding on probing, ≥ 5 mm clinical attachment level loss, and radiographic evidence of alveolar bone height loss, were undergoing periodontal maintenance therapy. Subjects had no history of myocardial infarction, angina, or stroke. Subjects also had to be willing to sign UNMC and Stony Brook Institutional Review Board-approved consent forms and had to be in good general health without co-morbidities that may interfere with adherence to the study protocol, planned follow-up or endpoint measurement • Exclusion criteria: allergy or hypersensitivity to tetracyclines; diseases or regular drug therapy that would affect the inflammatory or immune response (e.g., chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs)) or bone remodeling (e.g., prescription estrogens, bisphosphonates, calcitonin, and steroids); requirement for antibiotic premedication; diabetes; active periodontal therapy within the past year; normal bone mineral density (BMD) at both the lumbar spine and femoral neck (T-score above -1.0) or osteoporosis of the lumbar spine or femoral neck (T-score less than -2.5) • Participants: postmenopausal patients with chronic periodontitis and osteopenia of the lumbar spine or femoral neck • Number of participants: total 113; intervention group 51; control group 62 • Gender of participants: total male 0, female 113; intervention group 51/0; control group: 62/0 • Age of participants: total mean = 58.31; intervention group: 58.62$\pm$5.96 (SD); control group 58.06$\pm$5.73 • Lost to follow-up: the protocol was amended in April 2004, at which point 13 subjects had withdrawn consent (placebo n = 2, SDD n = 10) or had withdrawn (SDD n = 1) due to a serious adverse event, to allow measurement of inflammatory biomarkers in stored (-80°C) serum. 2 additional SDD subjects withdrew following the protocol amendment and refused to complete an exit exam that included the addendum study consent request. 53 subjects were randomised at Stony Brook; 46 Stony Brook subjects completed the trial and signed an addendum consent form to conduct additional serum analyses (ApoA-I and ApoA-II assessment) and serum was not collected from 1 subject at the 1 year visit
Interventions	<ul style="list-style-type: none"> • Intervention group: 20 mg doxycycline twice daily for 2 years (low-dose or subantimicrobial dose doxycycline; SDD) • Control group: a placebo look-alike twice daily for 2 years • All subjects received calcium and vitamin D supplements twice daily (a total of 1200 mg of calcium and 400 IU of vitamin D daily). Subjects were instructed not to take the study drug and calcium/vitamin D at the same time, being certain the supplements were taken at least 1 hour after taking the study drug. All subjects received periodontal maintenance every 3-4 months throughout the study, delivered by the subjects' own dental care providers and not by the study clinicians • Duration of follow-up: 24 months

Outcomes	<ul style="list-style-type: none"> • Serum hs-CRP (measured by ELISA-based assay, at baseline, 1 year and 2 years) • Total cholesterol, HDL-C and triglycerides (measured by ELISA-based assay, measured at baseline, 1 year and 2 years) • LDL, VLDL (measured by calculation, at baseline, 1 year and 2 years) • Serum ApoA-I and ApoA-II (measured by ELISA-based assay, at baseline, 1 year and 2 years) (Only the data from Stony Brook subjects were included because insufficient amounts of serum remained from the Nebraska subjects after completion of the biomarker analyses)
Notes	All the included participants were female and had osteopenia of the lumbar spine or femoral neck. The eligibility is not clear. Some data need confirmation from the authors and the eligibility needs further discussion

hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; RCT = randomised controlled trial; VLDL = very-low-density lipoprotein

Characteristics of ongoing studies [ordered by study ID]

Azhar 2010

Trial name or title	<ul style="list-style-type: none"> • Scientific title: influence of periodontal treatment on systemic inflammatory mediators: hsC-reactive protein, fibrinogen and white blood cells in CHD patients • Public title: influence of periodontal treatment on systemic inflammatory mediators perio-CHD
Methods	<ul style="list-style-type: none"> • Study type: parallel RCT • Randomisation: not clearly stated • Allocation concealment: not clearly stated • Blinding: single-blinded (investigator)
Participants	<ul style="list-style-type: none"> • Inclusion criteria: A) General/medical: 1) any race/ethnic group; 2) aged > 30 years; 3) male or female; 4) coronary heart disease (CHD) case confirmed by CHD angiography; 5) CHD diagnosed > 3 months prior to entry into study; 6) no acute or chronic systemic conditions (<i>see</i> exclusion criteria below); 7) no medications/medication history that can interfere with the study (<i>see</i> exclusion criteria below); 8) non-smoker (= never smoked) or former smoker (= does not smoke now and has not smoked at all for a minimum of the last 12 consecutive months); 9) able and willing to comply with study procedures; 10) able and willing to be available for the duration of the study; 11) able and willing to provide signed informed consent. B) Oral/periodontal: 1) dentate with at least 14 natural teeth, excluding third molars, which can be evaluated periodontally; 2) baseline whole mouth BOP > 20% of sites; 3) periodontitis case: periodontitis case defined as subject having ≥ 4 teeth with ≥ 1 site with PPD ≥ 4 mm and CAL ≥ 3 mm at same site; 4) no mechanical periodontal therapy in the last 6 months; 5) no acute oral diseases (mucosal lesions), oral infections, need for immediate dental/periodontal care (e.g., NUG) • Exclusion criteria: A) General/medical: 1) former smoker who does not smoke but who has smoked = 1 cigarette (or equivalent, in form of water pipe, pipe, cigar) in the last 12 months; 2) females pregnant or lactating; 3) systemic chronic conditions known to be associated with periodontitis or with changes in systemic inflammation: diabetes, rheumatoid arthritis, rheumatic fever, SLE, malignancy, respiratory diseases, renal diseases, other (e.g. autoimmune diseases, fungal infections, immunological deficiencies, etc.); 4) systemic acute conditions known to affect systemic markers of inflammation: acute bacterial infection,

	<p>acute viral infection (common cold, influenza, sinusitis), orthopaedic trauma, surgery; 5) medications known to affect systemic inflammatory biomarker: statins, systemic steroids, non-steroidal anti-inflammatory drugs, immunosuppressants; 6) medications potentially affecting systemic inflammatory markers, if therapy started less than 3 months prior to study such as hormone replacement therapy, contraceptives; 7) systemic antibiotic therapy in the last 3 months. B) Oral/periodontal: 1) BOP = 20% of sites; 2) topical/local antibiotic or anti-inflammatory therapy in last 6 months; 3) acute oral infections; 4) oral wounds, including recent (< 2 months) extractions</p> <ul style="list-style-type: none"> • Total number of participants: 317
Interventions	<ul style="list-style-type: none"> • Intervention group: SRP and oral hygiene instructions • Control group: no treatment • Follow-up: unclear
Outcomes	Changes in hs-CRP (the time of recording is unclear)
Starting date	July 2008
Contact information	<ul style="list-style-type: none"> • Person: Mohammad Azhar • Address: Punjab Institute of Cardiology • Country: Pakistan
Notes	Recruitment has finished

Haas 2013

Trial name or title	<ul style="list-style-type: none"> • Scientific title: periodontal therapy in coronary artery patients (PerioCardio) • Public title: periodontal therapy in coronary artery patients (PerioCardio)
Methods	<ul style="list-style-type: none"> • Study type: parallel RCT • Randomisation: mentioned but the detail was not clear • Allocation concealment: not clearly stated • Blinding: single-blinded (outcomes assessor)
Participants	<ul style="list-style-type: none"> • Inclusion criteria: 35-70 years coronary artery disease more than 10 teeth chronic periodontitis defined as 2 non-adjacent teeth with probing depth > 5 mm and periodontal attachment loss > 4 mm • Exclusion criteria: use of antibiotics in the last 6 months, periodontal therapy in the last 12 months • Total number of participants: 100
Interventions	<ul style="list-style-type: none"> • Intervention group: SRP under local anaesthesia + oral hygiene instruction and motivation • Control group: 1 session of supra-gingival calculus removal • Follow-up: 1 year
Outcomes	Changes of hs-CRP, HDL-C, LDL-C and total cholesterol levels (3, 6 months and 1 year after the treatment)
Starting date	January 2012

Haas 2013 (Continued)

Contact information	<ul style="list-style-type: none"> • Person: Haas • Address: Federal University of Rio Grande do Sul • Country: Brazil
Notes	

Skilton 2011

Trial name or title	<ul style="list-style-type: none"> • Scientific title: associations between periodontal disease and cardiovascular surrogate endpoints following periodontal treatment in an adult indigenous population with moderate/severe periodontal disease • Public title: associations between periodontal disease and cardiovascular surrogate endpoints in an adult indigenous population
Methods	<ul style="list-style-type: none"> • Study type: parallel RCT • Randomisation: after screening for periodontal disease, those with moderate or severe periodontal disease will be randomised on a 1:1 basis to either the treatment or control group. A computer generated permuted block randomisation sequence will be used, stratified by recruitment site (Darwin/Palmerston, Katherine) • Allocation concealment: not clearly stated • Blinding: the measurement of cardiovascular endpoints and the statistical analysis will be blinded
Participants	<ul style="list-style-type: none"> • Inclusion criteria: indigenous persons aged > 25 years that have lived in their current location for more than 2 years, and who plan to live at their current location for the next 2 years, with moderate/severe periodontal disease • Exclusion criteria: those with rheumatic heart disease history or other cardiac conditions requiring antibiotic prophylaxis for prevention of subacute bacterial endocarditis, or with obvious endodontic lesions or other sources of oral infection • Total number of participants: 266
Interventions	<ul style="list-style-type: none"> • Intervention group: SRP • Control group: no treatment • Follow-up: 1 year
Outcomes	hs-CRP, HDL-C, LDL-C, APO-A1, APO-B and total cholesterol (3 months and 1 year after the treatment)
Starting date	June 2010
Contact information	<ul style="list-style-type: none"> • Person: Lisa M Jamieson • Address: Australian Research Centre for Population Oral Health, School of Dentistry, University of Adelaide, Adelaide, Australia • Country: Australia
Notes	Registered (but retrospectively registered)

BOP = bleeding on probing; CAL = clinical attachment level; hs-CRP = high-sensitivity C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PPD = probing pocket depth; RCT = randomised controlled trial; SLE = systemic lupus erythematosus; SRP = scaling and root planing

DATA AND ANALYSES

Comparison 1. Secondary prevention: periodontal treatment versus community care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All cardiovascular events (25 months)	1	303	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.23, 2.22]
2 Serum hs-CRP (1 year)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Number of participants who had high hs-CRP (1 year)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Adverse events related to the treatment (25 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Secondary prevention: periodontal treatment versus community care, Outcome 1 All cardiovascular events (25 months).

Review: Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis

Comparison: 1 Secondary prevention: periodontal treatment versus community care

Outcome: 1 All cardiovascular events (25 months)

Analysis 1.2. Comparison 1 Secondary prevention: periodontal treatment versus community care, Outcome 2 Serum hs-CRP (1 year).

Review: Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis

Comparison: 1 Secondary prevention: periodontal treatment versus community care

Outcome: 2 Serum hs-CRP (1 year)

Analysis 1.3. Comparison 1 Secondary prevention: periodontal treatment versus community care, Outcome 3 Number of participants who had high hs-CRP (1 year).

Review: Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis

Comparison: 1 Secondary prevention: periodontal treatment versus community care

Outcome: 3 Number of participants who had high hs-CRP (1 year)

Analysis 1.4. Comparison 1 Secondary prevention: periodontal treatment versus community care, Outcome 4 Adverse events related to the treatment (25 months).

Review: Periodontal therapy for the management of cardiovascular disease in patients with chronic periodontitis

Comparison: 1 Secondary prevention: periodontal treatment versus community care

Outcome: 4 Adverse events related to the treatment (25 months)

ADDITIONAL TABLES

Table 1. Journals on stomatology for handsearching

Journal name	By ZD Shi et al	By CJ Li et al	By CJ Li and ZK Lv
<i>Chinese Journal of Stomatology</i>	1953 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>Stomatology</i>	1981 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>West China Journal of Stomatology</i>	1983 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>Journal of Practical Stomatology</i>	1985 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>Journal of Clinical Stomatology</i>	1985 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>Journal of Comprehensive Stomatology</i>	1985 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>Journal of Modern Stomatology</i>	1987 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>Chinese Journal of Conservative Dentistry</i>	1991 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>Journal of Maxillofacial Surgery</i>	1991 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>Shanghai Journal of Stomatology</i>	1992 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011

Table 1. Journals on stomatology for handsearching (Continued)

<i>Chinese Journal of Dental Material and Devices</i>	1992 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>Beijing Journal of Stomatology</i>	1993 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>Chinese Journal of Dental Prevention and Treatment</i>	1993 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>Chinese Journal of Orthodontics</i>	1994 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>Chinese Journal of Implantology</i>	1996 to Dec 2000	Jan 2001 to Dec 2009	Jan 2010 to May 2011
<i>Journal of International Stomatology</i>		Jan 2001 to Dec 2009	1974 to Dec 2000, Jan 2010 to May 2011
<i>Chinese Journal of Prosthodontics</i>		Jan 2001 to Dec 2009	1999 to Dec 2000, Jan 2010 to May 2011
<i>China Journal of Oral and Maxillofacial Surgery</i>		2003 to Dec 2009	Jan 2010 to May 2011
<i>Chinese Journal of Geriatric Dentistry</i>		2002 to Dec 2009	Jan 2010 to May 2011
<i>International Journal of Oral Science</i>			2009 to May 2011
<i>International Journal of Periodontics & Restorative Dentistry</i>			1981 to May 2011
<i>Journal of Clinical Periodontology</i>			1974 to May 2011
<i>Journal of Periodontal Research</i>			1966 to May 2011
<i>Journal of Periodontology</i>			1949 to May 2011
<i>Periodontology 2000</i>			1993 to May 2011

Table 2. Journals on cardiovascular disease for handsearching

Journal name	By CJ Li and ZK Lv
<i>Journal of Cardiovascular and Pulmonary Diseases</i>	1982 to May 2011
<i>Chinese Journal of Cardiology</i>	1973 to May 2011

Table 2. Journals on cardiovascular disease for handsearching (Continued)

<i>International Journal of Cerebrovascular Diseases</i>	1993 to May 2011
<i>Prevention and Treatment of Cardio-Cerebral-Vascular Disease</i>	2001 to May 2011
<i>Chinese Journal of Cerebrovascular Diseases</i>	2004 to May 2011
<i>Chinese Journal of Geriatric Heart Brain and Vessel Diseases</i>	1999 to May 2011
<i>Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease</i>	2003 to May 2011
<i>Practical Journal of Cardiac Cerebral Pneumal and Vascular Disease</i>	1993 to May 2011
<i>Circulation</i>	1950 to May 2011
<i>European Heart Journal</i>	1980 to May 2011
<i>Cardiovascular Research</i>	1967 to May 2011
<i>Circulation Research</i>	1953 to May 2011
<i>Cardiology</i>	1937 to May 2011
<i>Arteriosclerosis, Thrombosis, and Vascular Biology</i>	1981 to May 2011
<i>American Journal of Cardiology</i>	1958 to May 2011

APPENDICES

Appendix I. Cochrane Oral Health's Trials Register search strategy

From July 2013, searches of the Cochrane Oral Health Group's Trials Register were undertaken using the Cochrane Register of Studies and the search strategy below:

#1 ((cardiovascular or myocardial or heart* or coronar* or "artery disease*" or angina or "transient ischaemic attack*" or atherosclerosis or arteriosclerosis or "peripheral arterial disease*" or cerebrovascular or stroke* or ischemia or "intercranial hemorrhage" or "intercranial haemorrhage" or thrombosis or thromboses or aneurysm* or embolism* or DVT):ti,ab) AND (INREGISTER)

#2 ((periodont* or gingivitis or gingiva* or paradont*):ti,ab) AND (INREGISTER)

#3 (#1 and #2) AND (INREGISTER)

Previous searches were undertaken using the Procite software and the search strategy below:

((cardiovascular or myocardial or heart* or coronar* or "artery disease*" or angina or "transient ischaemic attack*" or atherosclerosis or arteriosclerosis or "peripheral arterial disease*" or cerebrovascular or stroke* or ischemia or "intercranial hemorrhage" or "intercranial haemorrhage" or thrombosis or thromboses or aneurysm* or embolism* or DVT) AND (periodont* or gingivitis or gingiva* or paradont*))

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

- #1. Exp CARDIOVASCULAR DISEASES
- #2. (myocardial or heart*) NEAR infarc*
- #3. heart NEAR (disease* or attack*)
- #4. (coronary NEAR (artery disease* or syndrome*))
- #5. (angina pectoris OR "transient ischaemic attack*")
- #6. exp ATHEROSCLEROSIS
- #7. (atherosclerosis OR arteriosclerosis)
- #8. "peripheral arterial disease"
- #9. exp CEREBROVASCULAR DISORDERS
- #10. (stroke* or (ischemia NEAR brain*) OR (infarc* NEAR brain*) OR "intercranial haemorrhage*" or "intercranial hemorrhage*")
- #11. exp THROMBOSIS
- #12. (thrombosis or occlusion* or thromboses or aneurysm* or embolism*)
- #13. (DVT):ti,ab
- #14. ("atheromatous plaque" or atheromata*)
- #15. #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
- #16. exp PERIODONTAL DISEASES
- #17. periodont*
- #18. (gingivitis or gingival*)
- #19. paradont*
- #20. #16 OR #17 OR #18 OR #19
- #21. exp PREVENTIVE DENTISTRY
- #22. Dental Care for Chronically Ill
- #23. exp PERIODONTICS
- #24. (scal* NEAR polish*)
- #25. (root* NEAR plan*)
- #26. (tooth NEAR scal*) OR (teeth NEAR scal*) OR (dental NEAR scal*)
- #27. (oral AND dental AND prophylaxis)
- #28. (gingivectomy OR gingivoplasty OR "subgingival curettage" OR subgingival curettage" OR "guided tissue regeneration")
- #29. Surgical flaps
- #30. "surgical flap"
- #31. ((#29 OR #30) AND periodont*)
- #32. (periodont* NEAR (therap* OR treat* OR surger*))
- #33. Oral Health
- #34. exp ORAL HYGIENE
- #35. (mouthrinse* OR mouth-rinse* OR "mouth rinse*" OR mouthwash* OR mouth-wash* OR "mouth wash*" OR toothbrush* OR "tooth brush*" OR tooth-brush* OR floss*)
- #36. exp DENTIFRICES
- #37. (dentifrice* OR toothpaste* OR tooth-paste* OR "tooth paste*")
- #38. Chlorhexidine
- #39. (chlorhexidine OR eludril OR chlorohex* or corsodyl)
- #40. exp ANTI-BACTERIAL AGENTS
- #41. (antibiotic* or anti-biotic* or antibacterial* or anti-bacterial*)
- #42. exp TETRACYCLINES
- #43. (tetracycline* OR doxycycline* OR minocycline* OR roxithromycin* OR moxifloxacin* OR ciprofloxacin* OR metronidazole*)
- #44. (PerioStat OR Atridox OR Elyzol OR PerioChip OR Arestin OR Actisite)
- #45. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR 41 OR #42 OR #43 OR #44
- #46. #15 AND #20 AND #45

Appendix 3. MEDLINE Ovid search strategy

1. exp Cardiovascular diseases/
2. ((myocardial or heart\$) adj5 infarc\$).mp.
3. (heart adj6 (disease\$ or attack\$)).mp.
4. (coronary adj6 (disease\$ or syndrome\$)).mp.
5. (angina or "transient ischaemic attack\$").mp.
6. exp Atherosclerosis/
7. (atherosclerosis or arteriosclerosis).mp.
8. "peripheral arterial disease".mp.
9. exp Cerebrovascular Disorders/
10. (stroke\$ or (ischemia adj3 brain\$) or (infarc\$ adj3 brain\$) or "intercranial haemorrhage\$" or "intercranial hemorrhage\$").mp.
11. exp Thrombosis/
12. (thrombosis or occlusion\$ or thromboses or aneurysm\$ or embolism\$).mp.
13. DVT.ti,ab.
14. ("atheromatous plaque" or atheromata\$).mp.
15. or/1-14
16. exp Periodontal Diseases/
17. periodont\$.mp.
18. (gingivitis or gingiva\$).mp.
19. paradont\$.mp.
20. or/16-19
21. exp Preventive Dentistry/
22. Dental Care for Chronically Ill/
23. exp Periodontics/
24. (scal\$ adj4 polish\$).mp.
25. (root\$ adj4 plan\$).mp.
26. ((tooth adj6 scal\$) or (teeth adj6 scal\$) or (dental adj6 scal\$)).mp.
27. (oral and dental and prophylaxis).mp.
28. (gingivectomy or gingivoplasty or "subgingival curettage" or "guided tissue regeneration").mp.
29. Surgical flaps/
30. "surgical flap\$".mp.
31. ((29 or 30) and periodont\$).mp.
32. (periodont\$ adj3 (therap\$ or treat\$ or surger\$)).mp.
33. Oral Health/
34. exp Oral Hygiene/
35. (mouthrinse\$ or mouth-rinse\$ or "mouth rinse\$" or mouthwash\$ or mouth-wash\$ or "mouth wash\$" or toothbrush\$ or "tooth brush\$" or tooth-brush\$ or floss\$).mp.
36. exp Dentifrices/
37. (dentifrice\$ or toothpaste\$ or tooth-paste\$ or "tooth paste\$").mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
38. Chlorhexidine/
39. (chlorhexidine or eludril or chlorohex\$ or corsodyl).mp.
40. exp Anti-bacterial agents/
41. (antibiotic\$ or anti-biotic\$ or antibacterial\$ or anti-bacterial\$).mp.
42. exp Tetracyclines/
43. (tetracycline\$ or doxycycline\$ or minocycline\$ or roxithromycin\$ or moxifloxacin\$ or ciprofloxacin\$ or metronidazole\$).mp.
44. (Periostat or Atridox or Elyzol or PerioChip or Arestin or Actisite).mp.
45. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46. 15 and 20 and 45

This subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity- maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of *The Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0 [updated March 2011] ([Lefebvre 2011](#)).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 4. Embase Ovid search strategy

1. exp Cardiovascular diseases/
2. ((myocardial or heart\$) adj5 infarc\$).mp.
3. (heart adj6 (disease\$ or attack\$)).mp.
4. (coronary adj6 (artery disease\$ or heart muscle ischemia)).mp.
5. (angina pectoris or "transient ischaemic attack\$").mp.
6. exp Atherosclerosis/
7. (atherosclerosis or arteriosclerosis).mp.
8. "peripheral arterial disease".mp.
9. exp Cerebrovascular Disorders/
10. (stroke\$ or (ischemia adj3 brain\$) or (infarc\$ adj3 brain\$) or "inter cranial haemorrhage\$" or "inter cranial hemorrhage\$").mp.
11. exp Thrombosis/
12. (thrombosis or occlusion\$ or "occlusive cerebrovascular disease" or aneurysm\$ or embolism\$).mp.
13. DVT.ti.ab.
14. ("atherosclerotic plaque" or atheroma\$).mp.
15. 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
16. exp Periodontal Diseases/
17. periodont\$.mp.
18. (gingivitis or gingiva\$).mp.
19. paradont\$.mp.
20. 16 or 17 or 18 or 19
21. exp Preventive Dentistry/
22. Dental Care for Chronically Ill/
23. exp Periodontics/
24. (scal\$ adj4 polish\$).mp.
25. (root\$ adj4 plan\$).mp.
26. ((tooth adj6 scal\$) or (teeth adj6 scal\$) or (dental adj6 scal\$)).mp.
27. (oral and dental and prophylaxis).mp.
28. (gingivectomy or gingivoplasty or "subgingival curettage" or "subgingival curettage" or "guided tissue regeneration").mp.
29. Surgical flaps/
30. "surgical flap\$".mp.
31. (29 or 30) and periodont\$.mp.
32. (periodont\$ adj3 (therap\$ or treat\$ or surger\$)).mp.
33. Oral Health/
34. exp Oral Hygiene/
35. (mouthrinse\$ or mouth-rinse\$ or "mouth rinse\$" or mouthwash\$ or mouth-wash\$ or "mouth wash\$" or toothbrush\$ or "tooth brush\$" or tooth-brush\$ or floss\$).mp.
36. exp Dentifrices/
37. (dentifrice\$ or toothpaste\$ or tooth-paste\$ or "tooth paste\$").mp.

38. Chlorhexidine/
 39. (chlorhexidine or eludril or chlorohex\$ or corsodyl).mp.
 40. exp Anti-bacterial agents/
 41. (antibiotic\$ or anti-biotic\$ or antibacterial\$ or anti-bacterial\$).mp.
 42. exp Tetracyclines/
 43. (tetracycline\$ or doxycycline\$ or minocycline\$ or roxithromycin\$ or moxifloxacin\$ or ciprofloxacin\$ or metronidazole\$).mp.
 44. (Periostat or Atridox or Elyzol or PerioChip or Arestin or Actisite).mp.
 45. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39. or 40 or 41 or 42 or 43 or 44
 46. 15 and 20 and 45
- The above subject search was linked to adapted version of the Cochrane Embase Project filter for identifying RCTs in Embase Ovid (see <http://www.cochranelibrary.com/help/central-creation-details.html> for information):
1. Randomized controlled trial/
 2. Controlled clinical study/
 3. Random\$.ti,ab.
 4. randomization/
 5. intermethod comparison/
 6. placebo.ti,ab.
 7. (compare or compared or comparison).ti.
 8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
 9. (open adj label).ti,ab.
 10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
 11. double blind procedure/
 12. parallel group\$1.ti,ab.
 13. (crossover or cross over).ti,ab.
 14. ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab.
 15. (assigned or allocated).ti,ab.
 16. (controlled adj7 (study or design or trial)).ti,ab.
 17. (volunteer or volunteers).ti,ab.
 18. trial.ti.
 19. or/1-18
 20. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
 21. 19 not 20

Appendix 5. CINAHL EBSCO search strategy

- S1 MH Cardiovascular diseases
- S2 (myocardial or (heart* N5 infarc*))
- S3 (heart N6 disease* or attack*)
- S4 (coronary N6 disease* or syndrome*)
- S5 (angina or "transient ischaemic attack*")
- S6 MH Atherosclerosis
- S7 (atherosclerosis or arteriosclerosis)
- S8 "peripheral arterial disease"
- S9 MH Cerebrovascular Disorders
- S10 (stroke* or (ischemia N3 brain*) or (infarc* N3 brain*) or intracranial haemorrhage* or intracranial hemorrhage*)
- S11 MH Thrombosis
- S12 (thrombosis or occlusion* or thromboses or aneurysm* or embolism*)
- S13 TI DVT or AB DVT
- S14 ("atheromatous plaque" or "atherosclerotic plaque" or atheromata*)
- S15 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14
- S16 MH Periodontal Diseases

S17 periodont*
 S18 (gingivitis or gingival*)
 S19 paradont*
 S20 S16 or S17 S18 or S19
 S21 MH Preventive Dentistry
 S22 Dental Care for Chronically Ill
 S23 MH Periodontics
 S24 (scal* N4 polish*)
 S25 (root* N4 plan*)
 S26 (tooth N6 scal*) or (teeth N6 scal*) or (dental N6 scal*)
 S27 oral and dental and prophylaxis
 S28 (gingivectomy or gingivoplasty or subgingival curettage* or guided tissue regeneration)
 S29 Surgical flaps
 S30 "surgical flap*" ⁴⁴
 S31 ((S29 or S30) and periodont*)
 S32 (periodont* N3 therap* or treat* or surger*)
 S33 Oral Health
 S34 MH Oral Hygiene
 S35 (mouthrinse* or mouth-rinse* or "mouth rinse*" or mouthwash* or mouth-wash* or "mouth wash*" or toothbrush* or "tooth brush*" or tooth-brush* or floss*)
 S36 MH Dentifrices
 S37 (dentifrice* or toothpaste* or tooth-paste* or "tooth paste*" ⁴⁴)
 S38 Chlorhexidine
 S39 (chlorhexidine or eludril or chlorohex* or corsodyl)
 S40 Anti bacterial agents
 S41 (antibiotic* or anti-biotic* or antibacterial* or anti-bacterial*)
 S42 Tetracyclines
 S43 (tetracycline* or doxycycline* or minocycline* or roxithromycin* or moxifloxacin* or ciprofloxacin* or metronidazole*)
 S44 (PerioStat or Atridox or Elyzol or PerioChip or Arestin or Actisite)
 S45 S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44
 S46 S15 and S20 and S45
 The above subject search was linked to Cochrane Oral Health's filter for CINAHL EBSCO:
 S1 MH Random Assignment or MH Single-blind Studies or MH Double-blind Studies or MH Triple-blind Studies or MH Crossover design or MH Factorial Design
 S2 TI ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study") or AB ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study") or SU ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study")
 S3 TI random* or AB random*
 S4 AB "latin square" or TI "latin square"
 S5 TI (crossover or cross-over) or AB (crossover or cross-over) or SU (crossover or cross-over)
 S6 MH Placebos
 S7 AB (singl* or doubl* or trebl* or tripl*) or TI (singl* or doubl* or trebl* or tripl*)
 S8 TI blind* or AB mask* or AB blind* or TI mask*
 S9 S7 and S8
 S10 TI Placebo* or AB Placebo* or SU Placebo*
 S11 MH Clinical Trials
 S12 TI (Clinical AND Trial) or AB (Clinical AND Trial) or SU (Clinical AND Trial)
 S13 S1 or S2 or S3 or S4 or S5 or S6 or S9 or S10 or S11 or S12

Appendix 6. OpenGrey search strategy

(periodont* or paradont*) AND cardiovascular
(periodont* or paradont*) AND heart*
(periodont* or paradont*) AND stroke*
(periodont* or paradont*) AND coronar*

Appendix 7. US National Institutes of Health Trials Register (ClinicalTrials.gov) search strategy

cardiovascular AND periodontitis
heart AND periodontitis
stroke AND periodontitis
coronary AND periodontitis

Appendix 8. WHO International Clinical Trials Registry Platform search strategy

cardiovascular AND periodont*
stroke AND periodont*
"heart disease" AND periodont*
coronar* AND periodont*

Appendix 9. Chinese BioMedical Literature Database search strategy

1. 主题词:心血管疾病/全部树/全部副主题词 -限定:-
2. 主题词:牙周疾病/全部树/全部副主题词 -限定:-
3. 中文摘要:随机 -限定:-
4. #1 and #2 and #3 -限定:-

Appendix 10. China National Knowledge Infrastructure search strategy

(((摘要=心血管 或者 摘要=心脏) 并且 主题=牙周) 并且 摘要=随机) (精确匹配), 专辑导航: 全部; 数据库: 文献 跨库检索

Appendix 11. VIP search strategy

题名或关键词=牙周 并且 题名或关键词=心脏 并且 文摘=随机

Appendix 12. Sciencepaper Online search strategy

题目 =牙周 与 (题目 =心脏 或 题目 =心血管) 与 摘要=随机

WHAT'S NEW

Last assessed as up-to-date: 27 August 2017.

Date	Event	Description
26 September 2017	New citation required but conclusions have not changed	Conclusions remain the same as we did not identify any new studies for inclusion
23 September 2017	New search has been performed	Search updated. No new studies included. New information added in background and discussion

CONTRIBUTIONS OF AUTHORS

- Chunjie Li and Zongkai Lv proposed this clinical question, registered the title with Cochrane Oral Health.
- Drafting and revising of the protocol: Chunjie Li, Zongkai Lv, Ye Zhu, Yafei Wu and Longjiang Li.
- Searching of Chinese databases: Chunjie Li.
- Study identification: Chunjie Li and Zongkai Lv.
- Data extraction and risk of bias assessment: Chunjie Li and Zongkai Lv.
- Data management and data analysis: Chunjie Li.
- Data interpreting: Yafei Wu and Ye Zhu.
- Drafting/Updating the systematic review: Chunjie Li.
- Revising of the updated systematic review: Zongkai Lv, Ye Zhu, Yafei Wu, Longjiang Li and Zipporah Iheozor-Ejiofor.

DECLARATIONS OF INTEREST

- Chunjie Li was supported by the 2011 Aubrey Sheiham Public Health & Primary Care Scholarship and finished the systematic review at the UK Cochrane Centre. We declare that the scholarship had no impact on the review content.
- Zongkai Lv, Zongdao Shi, Ye Zhu, Yafei Wu, Longjiang Li, Zipporah Iheozor-Ejiofor: no interests to declare.

SOURCES OF SUPPORT

Internal sources

- West China College of Stomatology, Sichuan University, China.
- Chinese Cochrane Center, China.
- National University Student Innovation Test Plan, China.

Grant Number: 101061001

- Aubrey Sheiham Public Health & Primary Care Scholarship 2011, UK.
- School of Dentistry at The University of Manchester, Manchester Academic Health Sciences Centre (MAHSC) and the NIHR Manchester Biomedical Research Centre, UK.

External sources

- Cochrane Oral Health Global Alliance, UK.

The production of Cochrane Oral Health reviews has been supported financially by our Global Alliance since 2011 (ohg.cochrane.org/partnerships-alliances). Contributors over the past year have been: British Association for the Study of Community Dentistry, UK; British Society of Paediatric Dentistry, UK; the Canadian Dental Hygienists Association, Canada; Centre for Dental Education and Research at All India Institute of Medical Sciences, India; National Center for Dental Hygiene Research & Practice, USA; New York University College of Dentistry, USA; NHS Education for Scotland, UK; Swiss Society for Endodontology, Switzerland.

- UK Cochrane Centre, UK.
- National Institute for Health Research (NIHR), UK.

This project was supported by the NIHR, via Cochrane Infrastructure funding to Cochrane Oral Health. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- In the inclusion criteria, the depth of the periodontal pockets was changed from 5 mm to 4 mm. This decision was based on clinical expert advice to shift focus from the severity to any clinical diagnosis of periodontitis.
- The following exclusion criteria: 'patients with severe systemic diseases other than cardiovascular disease, who are pregnant, lactating or unable to return for follow-up' and 'studies not focusing on primary or secondary prevention' were added to the review as they were erroneously omitted from the protocol.
- 'Follow-up time of one year or longer' was added to the types of studies as suggested by Cochrane Oral Health.
- Heart function parameters (such as ejection fraction, etc.) were added as a secondary outcome considering the aims of this review.
- The Cochrane Heart Group's Trials Register was not searched as all trials in the register were also available in CENTRAL.
- The US National Institutes of Health Trials Register was added to the search in accordance with the new standards for the conduct of Cochrane systematic reviews (Methodological standards for the conduct of new Cochrane intervention reviews (MECIR) version 2.3).
- The description of the seven domains used for risk of bias assessment changed (as the *Cochrane Handbook for Systematic Reviews of Interventions* evolved from version 5.0 to 5.1), but the essence stayed exactly the same.

INDEX TERMS

Medical Subject Headings (MeSH)

Cardiovascular Diseases [etiology; *prevention & control]; Chronic Periodontitis [complications; *therapy]; Coronary Disease [etiology; prevention & control]; Dental Scaling; Randomized Controlled Trials as Topic; Root Planing; Secondary Prevention [methods]

MeSH check words

Humans