The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: A meta-analysis

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Chicago, IL

Background Previous studies have shown conflicting results as to whether periodontitis (PD) is associated with increased risk of coronary heart disease (CHD). The aim of the current study was to evaluate whether such an association exists.

Methods A systematic review of the literature revealed 5 prospective cohort studies (follow-up >6 years), 5 case-control studies, and 5 cross-sectional studies that were eligible for meta-analysis. Individual studies were adjusted for confounding factors such as age, sex, diabetes mellitus, and smoking. The 3 study categories were analyzed separately. Heterogeneity of the studies was assessed by Cochran Q test. The studies were homogeneous; therefore, the Mantel-Haenszel fixed-effect model was used to compute common relative risk and odds ratio (OR).

Results Meta-analysis of the 5 prospective cohort studies (86,092 patients) indicated that individuals with PD had a 1.14 times higher risk of developing CHD than the controls (relative risk 1.14, 95% CI 1.074-1.213, \( p < .001 \)). The case-control studies (1,423 patients) showed an even greater risk of developing CHD (OR 2.22, 95% CI 1.59-3.117, \( p < .001 \)). The prevalence of CHD in the cross-sectional studies (17,724 patients) was significantly greater among individuals with PD than in those without PD (OR 1.59, 95% CI 1.32-1.907, \( p < .001 \)). When the relationship between number of teeth and incidence of CHD was analyzed, cohort studies showed 1.24 times increased risk (95% CI 1.14-1.36, \( p < .0001 \)) of development of CHD in patients with <10 teeth.

Conclusions This meta-analysis indicates that both the prevalence and incidence of CHD are significantly increased in PD. Therefore, PD may be a risk factor for CHD. Prospective studies are required to prove this assumption and evaluate risk reduction with the treatment of PD. (Am Heart J 2007;154:830-7.)

Periodontal disease is defined as chronic inflammation of gum tissue, including the ligaments and bony structures that hold the tooth in place. A study done in the late 1980s by Simonka et al.¹ showed that patients with myocardial infarction had a higher prevalence of periodontal disease. Since then, there has been a variety of literature studying the association between poor oral health and cardiovascular disease (CVD). Immunostainings of carotid endarterectomy specimens have shown the presence of 2 major odontopathogens, Porphyromonas gingivalis and Streptococcus sanguis, in atherosclerotic plaques.² Thus, the release of bacteria and proinflammatory mediators such as bacterial endotoxins and cytokines in the bloodstream that causes the release of acute phase reactants (such as C-reactive protein) leading to increased inflammatory activity in atherosclerotic lesions may represent the link between periodontal infection and CVD.³,⁴

Since the late 1980s, a number of cross-sectional, case-control, and longitudinal studies have reported that periodontitis (PD) may be associated with cardiovascular events. However, some of these studies have reported no significant association. These conflicting results may arise from various strong confounding factors associated with the CVD such as age, sex, diabetes mellitus (DM), smoking, and family history. Understanding these factors at every point of epidemiologic study is important to avoid potential biases particularly when the association under investigation is already presumed to be weak.⁵

The purpose of this study is to determine the relationship between periodontal disease and coronary heart disease (CHD) by gathering information from the individual studies and using meta-analysis techniques.

Materials and methods

Literature search and study selection

Literature searches were done by investigators (A.B. and R.A.) using the PubMed computerized database (1966-2006), Cochrane...
Table I. Details of the cohort studies included in the metanalysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Assessment of oral health</th>
<th>Cardiovascular assessment</th>
<th>Follow-up (y)</th>
<th>Variables controlled</th>
<th>Study quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeStefano et al 1993</td>
<td>9760 men and women aged 25-74 y</td>
<td>No. of decayed teeth, gingivitis with or without pockets, grade 4 pockets</td>
<td>Admission to hospital, death from CAD</td>
<td>14</td>
<td>Age, sex, race, BMI, systolic BP, education, poverty, diabetes, marital status, smoking, physical activity, alcohol, cholesterol</td>
<td>Good</td>
</tr>
<tr>
<td>Mattila et al 1995</td>
<td>214 individuals with CAD, mean age 49 y</td>
<td>Total dental index ranging from 0 to 10 and pantomography index</td>
<td>Hospitalization due to nonfatal MI or unstable angina, death due to CAD</td>
<td>7.2</td>
<td>Age, sex, socioeconomic status, smoking, HTN, diabetes, BMI, serum lipids, number of previous MI</td>
<td>Good</td>
</tr>
<tr>
<td>Joshipura et al 1996</td>
<td>44,119 male health professionals aged 40-75 y</td>
<td>Self-reported PD, no. of teeth present</td>
<td>Fatal and nonfatal MI, sudden death</td>
<td>6</td>
<td>Age, BMI, exercise, smoking habits, alcohol consumption, family history of MI before age 60 y, vitamin E intake</td>
<td>Fair</td>
</tr>
<tr>
<td>Wu et al 2000</td>
<td>9962 adults aged 25-74 y</td>
<td>No periodontal disease, gingivitis (inflammation and pocket formation), PD (4 or more teeth with pocket), edentulousness</td>
<td>CVD, CHD, stroke</td>
<td>10</td>
<td>Sex, race, education, poverty index, diabetes, HTN, smoking, alcohol use, BMI, cholesterol</td>
<td>Good</td>
</tr>
<tr>
<td>Howell et al 2001</td>
<td>22,037 US male physicians aged 40-84 y</td>
<td>Self-reported periodontal disease</td>
<td>Nonfatal MI (WHO criteria), nonfatal stroke, death due to cardiovascular cause</td>
<td>12.3</td>
<td>Age, aspirin or β-carotene treatment assignment, cigarette smoking, alcohol use, BMI, physical activity, DM, BP</td>
<td>Fair</td>
</tr>
</tbody>
</table>

BMI, Body mass index; BP, blood pressure; HTN, hypertension; MI, myocardial infarction; WHO, World Health Organization.

Controlled Trials Register (1970-2006), EMBASE (1980-2006), and CINAHL (1982-2006). The search was restricted to the articles including human subjects. In addition, manual searches were performed through the reference lists of published articles and review papers. Any unpublished studies were excluded.

For oral pathology, the following terms were used: periodontal disease, tooth diseases, gingivitis, and chronic periodontal infections.

For heart disease, the following terms were used: coronary artery disease, cardiovascular disease, atherosclerosis, and stroke.

Inclusion criteria used for the current meta-analysis were the following:

1. Research articles with sample size >80
2. Studies defining cases as people with fatal or nonfatal coronary artery disease (CAD)
3. Studies defining periodontal disease either by clinical assessment of oral health or by self-reported periodontal disease
4. Studies providing sufficient information for the calculation of relative risk (RR) and odds ratio (OR), as well as those studies that readily provided these or other accepted risk estimates

Exclusion criteria were the following:

1. Studies done on animals
2. Duplicate studies (studies originating from the same subjects by the same investigators but published in different journals)
3. Studies providing association between different markers of CAD or particular pathogens involved in PD
4. Letters to editors, unpublished articles, and articles providing insufficient information to calculate the RR or OR
5. Prospective studies calculating OR and hazard ratio instead of RR

Two investigators (R. A. and A. B.) independently reviewed the searched articles. Final decision about inclusion or exclusion was made by mutual agreement. Applying the search terms, 320 articles were identified, out of which 27 articles were found to be relevant. After applying the inclusion and exclusion criteria, 20 articles remained eligible for meta-analysis. Among the 20 articles, there were 10 prospective cohort studies, 5 case-control studies, and 5 cross-sectional studies. It was decided that these 3 study categories would be analyzed separately. Most of these studies reported their result as a risk estimate (RR or OR), but did not provide the basic data used for computation. This prevented us to compute a uniform type of risk estimate for each of these studies. Although using computed risk estimates for meta-analysis is legitimate, RR and OR represent different approaches of risk estimations and combining them in the same quantitative meta-analysis may not be appropriate. Because of the mismatch between studies in the type of risk estimates and the lack of basic data to compute uniform risk estimates across the studies, only 15 of the 20 eligible studies were used for quantitative meta-analysis: 5 prospective cohort studies reporting RR (follow-up >6 years), 5 case-control studies, and 5 cross-sectional studies, all of which reported OR.

Data extraction

Using a standard protocol, the 2 investigators (R. A. and A. B.) collected the following data from the research articles: name of
the authors, name of the journal, date of publication, sample size, study design, demographic characteristics of the population, years of follow-up, and outcome of the study. In addition, how well the studies were adjusted for confounding variable and whether the outcomes were measured in a standard, valid, and reliable way were assessed. Most of the studies included in this meta-analysis had adjusted for known cardiovascular risk factors such as age, sex, cholesterol, diabetes, hypertension, smoking, and body weight.

The predictor variable was periodontal disease, which included both PD and gingivitis. The definitions of PD and gingivitis were taken from the articles included in our study. Some studies measured the predictor variable by clinical examination such as probing the pocket depth, papillary bleeding score, attachment loss, bone loss, and gingival recession. Other studies performed visual inspection of the oral cavity looking for swollen and red papillae, bleeding gums, plaque and calculus indices, number of missing teeth, and edentulousness. The remaining studies relied on the self-reported oral health and history of periodontal disease. Although clinical assessment of periodontal disease offers a more reliable estimation of the severity of periodontal disease and its classification (gingivitis and PD), we recognized that self-reported oral health could adequately provide an approximate assessment of severity of periodontal disease.

The outcome variable was defined as CHD that includes both fatal and nonfatal CHD. We did not consider stroke as a separate outcome variable. However, in some studies, the outcome variable was CVD inclusive of ischemic stroke. We included these studies in our analysis because the pathophysiology of ischemic stroke is essentially different from hemorrhagic stroke and includes thromboembolic process, platelet aggregation, and increased fibrinogen, all of which are shown to be caused by periodontal infection.

Two investigators (R. A. and A. B.) used the criteria developed by the US Preventive Services Task Force to determine internal validity of the individual studies included in the meta-analysis. Studies were rated in 3 categories (“good,” “fair,” and “poor”) on the basis of these criteria (Tables I-III).

### Statistical methods

A systematic review of the literature revealed 5 prospective cohort studies (follow-up >6 years), 5 case-control studies, and 5 cross-sectional studies that were eligible for meta-analysis. Individual studies were adjusted for confounding factors such as age, sex, DM, and smoking. The 3 study categories were analyzed separately. The statistical analysis was performed by the Comprehensive Meta-Analysis software package (version CM 2.2, Biostat, Englewood, NJ). Heterogeneity of the studies was assessed by Cochran Q test. The studies were homogeneous; therefore, the Mantel-Haenszel fixed-effect model was used to compute common RR and OR. A 2-sided alpha error <.05 was considered to be significant.

The effect of number of teeth on the risk of CHD was assessed on the number of teeth (0-10, 11-16, and 17-24 teeth). The applied statistics required that

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Assessment of oral health</th>
<th>Cardiovascular assessment</th>
<th>Variables controlled</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loesch et al 1998</td>
<td>320 veterans aged &gt;60 y from VA hospital and long-term care facility</td>
<td>Oral examination assessing no. of missing teeth, plaque benzoyl-di-arginine-naphthylamide test scores, salivary levels of S sanguis, xerostomia</td>
<td>Review of subject’s medical records and documentation of established MI, CABG, clinical angina, ECG, serum enzyme levels, angiography, BP, and cholesterol values</td>
<td>DM, smoking history, current use of alcohol, age, BMI, BP, cholesterol</td>
<td>Good</td>
</tr>
<tr>
<td>Arbes et al 1999</td>
<td>5564 people aged 40 y and older</td>
<td>Dental examination measuring the percentage of periodontal sites per person with attachment loss of 3 mm or greater</td>
<td>Self-reported history of MI</td>
<td>Age, sex, race, poverty, smoking, diabetes, high BP, BMI, and serum cholesterol</td>
<td>Fair</td>
</tr>
<tr>
<td>Buhlin et al 2002</td>
<td>2839 people aged 20-84 y</td>
<td>Mailed questionnaire asking about the bleeding gums and pockets around teeth</td>
<td>Mailed questionnaire asking if the participant had any type of CVD in last 9 y</td>
<td>Age, sex, smoking, education, civil status, and income</td>
<td>Fair</td>
</tr>
<tr>
<td>Buhlin et al 2003</td>
<td>723 participants aged 20-84 y</td>
<td>Mailed questionnaire asking about the bleeding gums and deep pockets around teeth</td>
<td>Self-reported CVD during last 9 y</td>
<td>DM, sex, age, and tobacco use</td>
<td>Fair</td>
</tr>
<tr>
<td>Elter et al 2004</td>
<td>8363 men and women aged 52-75 y</td>
<td>Dental examination measuring the probing depth, cementoenamel junction measures</td>
<td>History of MI or revascularization procedures at the ARIC baseline examination or incident of CHD during the 9-y follow-up</td>
<td>Smoking status and intensity, has a current dentist, HTN, DM, BMI, triglycerides, LDL-C, and HDL-C</td>
<td>Good</td>
</tr>
</tbody>
</table>

VA, Veterans Affairs; CABG, coronary artery bypass graft; ECG, electrocardiogram; ARIC, Atherosclerosis Risk in Communities; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
categorical variables (number of teeth) be transformed to numerical (continuous) variables, which was performed by using the median number of teeth for each of the 3 categories. First, a linear regression analysis was performed to evaluate the correlation (Pearson) between the median number of teeth and the corresponding RRs, followed by a meta-regression analysis that used log-transformed risk estimates.

**Table III. Details of case-control studies included in the meta-analysis**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Assessment of oral health</th>
<th>Cardiovascular assessment</th>
<th>Variables controlled</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malthaner et al 2002(^{18})</td>
<td>Nonsmoking and nondiabetic patients older than 40 y with no history of MI in past 6 m and who had undergone cardiac catheterization in past 12 m</td>
<td>Periodontal examination evaluating clinical attachment level and also radiographic analysis assessing radiographic bone level</td>
<td>Angiographically confirmed CAD. Cases: 50% stenosis in at least 1 major epicardial artery. Controls: &lt;50% stenosis in all identified arteries</td>
<td>Adjusted for age and previous smoking status</td>
<td>Fair</td>
</tr>
<tr>
<td>Geerts et al 2004(^{19})</td>
<td>108 CAD patients and 62 healthy controls</td>
<td>Probing depth, periodontal pocket bleeding index, plaque index, and tooth mobility</td>
<td>Cases: 108 patients treated for CAD. 62 healthy controls with similar mean age group</td>
<td>Age, sex, smoking, alcohol intake, diet, physical activity, HTN, diabetes, hyperlipidemia</td>
<td>Good</td>
</tr>
<tr>
<td>Buhlin et al 2005(^{20})</td>
<td>143 women aged 43-79 y with CHD and 50 women aged 45-77 y without CHD</td>
<td>Dental examination measuring probing depth score, hygiene index, restoration, and dental caries. Digital panoramic radiographs measuring bone height</td>
<td>Cases: CHD patients who were treated for MI, PTCA, and CABG in 2 large hospitals. Controls: women with no history of CHD</td>
<td>Smoking, academic achievement, alcohol consumption, unemployment, ability to maintain the body weight, regular exercise, ability to relax daily, having a hobby or pastime, plaque, and C-reactive protein</td>
<td>Good</td>
</tr>
<tr>
<td>Briggs et al 2006(^{21})</td>
<td>Cases were men aged 40 y and older with angiographically proven CHD, and controls were age-matched men.</td>
<td>Measurement of plaque, bleeding on probing, probing depth measurement</td>
<td>Cases were men with proven CAD confirmed by &gt;50% narrowing of at least one coronary artery at coronary angiography. Controls were the random sample of age-matched men from the same locality.</td>
<td>Smoking, academic achievement, alcohol consumption, unemployment, ability to maintain the body weight, regular exercise, ability to relax daily, having a hobby or pastime, plaque, and C-reactive protein</td>
<td>Good</td>
</tr>
<tr>
<td>Spahr et al 2006(^{22})</td>
<td>263 angiographically confirmed CHD subjects and 526 age- and sex-matched controls without history of CHD</td>
<td>A modified CPITN measured at 6 sites of each tooth</td>
<td>Cases had at least 1 stenosis that was 50% or more of the luminal diameter of a major coronary artery.</td>
<td>Good smoking, alcohol consumption, DM, HTN, hyperlipoproteinemia, age, sex, BMI, diabetes, education, place of birth</td>
<td></td>
</tr>
</tbody>
</table>

PTCA, Percutaneous transluminal coronary angioplasty; CPITN, Community Periodontal Index of Treatment Needs.

**Results**

As shown in [Figure 1](#), meta-analysis of the 5 prospective cohort studies (86092 patients) indicated that individuals with PD had a 1.14 times higher risk of developing CHD than the controls (95% CI 1.074-1.213, \( P < .001 \)). DeStefano et al\(^{9}\), Mattila et al\(^{10}\), and Wu et al\(^{12}\) found that this risk ratio is significant. However, Howell et al\(^{13}\) and Joshipura et al\(^{11}\) found that this risk ratio was not significant. One of the possible explanations they provide for the negative results is that some of the earlier studies including that of DeStefano et al\(^{9}\) were not adequately adjusted for smoking, which is considered one of the major contributing factor for developing CHD. However, Joshipura et al\(^{11}\) did show a strong effect of tooth loss on overall incidence of CHD. They appreciate that tooth loss is a marker of severe periodontal disease that was not very well indicated by their dental assessment, and they do not completely exclude the possibility of a small increase in the risk of CHD due to periodontal disease. Nevertheless, we believe that all the studies included in our meta-analysis were well adjusted for all the major confounding factors contributing to CHD. We did not correct for any confounding factors for our analysis. Each study showed a trend toward higher risk with periodontal disease, and other studies provided enough power for yielding a significant difference.

A meta-analysis of cross-sectional studies (17724 patients) indicated that prevalence of CHD is 1.59 times higher (95% CI 1.329-1.907, \( P < .001 \)) in patients with PD as compared with the people who do not have PD. Out of 5 studies considered here, only one study, namely, that of Arbes et al\(^{15}\) found that this effect is not significant (Figure 2).
Five case-control studies (1423 patients) qualified for our meta-analysis. The results indicated that there is an even greater risk of developing CHD (OR 2.22, 95% CI 1.59-3.117, \( P < .001 \)) among patients with periodontal disease. Except for the study of Malthaner et al, all the individual studies showed a significant increase in CHD among patients with periodontal disease as compared with controls (Figure 3).

We also looked at the relation between number of teeth and incidence of CHD. We found 3 cohort studies that looked at the effect of edentulousness (number of teeth <10) on CHD. It is observed that there is 1.24 times increased risk (95% CI 1.14-1.36, \( P < .0001 \)) of development of CHD in patients who have <10 teeth as compared with healthy adults (Figure 4).

Greater than 10 teeth was not associated with a significantly higher risk of CHD in this analysis. However, the trends indicate that an inverse relationship between the number of teeth and the risk of CHD may exist. Three cohort studies provided a total of 5 point estimates for the evaluation of this relationship. Regression analysis showed a trend toward a higher risk of CHD with decreasing number of teeth but did not reach statistical significance (\( R = -0.639, P = .243 \)). Meta-regression analysis performed on log-transformed RR resulted in a better model to describe the association between the number of teeth and RR of CHD (\( P = .09 \), showing a negative slope and a point estimate for log RR of 0.278 for zero tooth (95% CI 0.1461-0.4097, \( P < .001 \)). This log RR can be translated to an RR of 1.32 (Figure 5).

Discussion
Our results indicate that there is a statistically significant positive correlation between periodontal disease and CHD. Both the incidence and prevalence of CHD are increased in patients who are affected with periodontal disease.
Coronary heart disease is a multifactorial disease. Various risk factors such as age, sex, family history of heart disease, smoking, alcohol intake, DM, exercise, obesity, and high blood pressure play a role in the pathogenesis of CHD. Most of the studies included in the analysis have adjusted for these confounding factors. Some of the studies had included various other confounding factors. For example, the studies by DeStefano et al and Arbes et al also included race, education, and socioeconomic status. Socioeconomic status and level of education have been shown to have a strong correlation with CVD. In addition, some of the studies have also adjusted for the factors such as vitamin E intake, ability to relax daily, having a hobby or pastime, and C-reactive protein level. This could be considered as overadjustment because although some of these factors are related to CHD, they may not have any impact on periodontal disease per se. In such cases, they are not considered as true confounders. Nevertheless, no changes in these overadjustments were made in our analysis. All the individual studies were adjusted for age and sex. Although the study of Malthaner et al included sex as one of the confounding factor, in the final analysis, only age and previous smoking status were considered.

### Figure 3

**Odds Ratio of Periodontitis for CHD: Case Control Studies**

<table>
<thead>
<tr>
<th>Model</th>
<th>Study name</th>
<th>Subjects</th>
<th>Statistics for each study</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Briggs (22)</td>
<td>N = 171</td>
<td>3.060</td>
<td>1.021</td>
<td>9.175</td>
</tr>
<tr>
<td>Buhlin (21)</td>
<td>N = 193</td>
<td>3.800</td>
<td>1.666</td>
<td>8.667</td>
</tr>
<tr>
<td>Geerts (20)</td>
<td>N = 170</td>
<td>6.500</td>
<td>1.818</td>
<td>23.235</td>
</tr>
<tr>
<td>Malthaner SC (19)</td>
<td>N = 100</td>
<td>1.635</td>
<td>0.465</td>
<td>5.751</td>
</tr>
<tr>
<td>Spahr (23)</td>
<td>N = 789</td>
<td>1.670</td>
<td>1.080</td>
<td>2.581</td>
</tr>
<tr>
<td>Fixed Overall</td>
<td>N = 1,423</td>
<td>2.226</td>
<td>1.590</td>
<td>3.117</td>
</tr>
</tbody>
</table>

Odds ratio of periodontitis for coronary heart disease: case-control studies.

### Figure 4

**Number of Teeth and the Relative Risk of CHD**

<table>
<thead>
<tr>
<th>Group by</th>
<th>Study name</th>
<th>Number of Teeth</th>
<th>Subjects</th>
<th>Statistics for each study</th>
<th>Risk ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Joshipura (11)</td>
<td>0 to 10 Teeth</td>
<td>N = 44119</td>
<td>1.200</td>
<td>0.362</td>
</tr>
<tr>
<td></td>
<td>Wu (12)</td>
<td>0 to 10 Teeth</td>
<td>N = 9992</td>
<td>1.220</td>
<td>1.111</td>
</tr>
<tr>
<td></td>
<td>Morrison (24)</td>
<td>0 to 10 Teeth</td>
<td>N = 10366</td>
<td>1.006</td>
<td>1.167</td>
</tr>
<tr>
<td></td>
<td>Joshipura (11)</td>
<td>11 to 16 Teeth</td>
<td>N = 44119</td>
<td>1.060</td>
<td>0.720</td>
</tr>
<tr>
<td></td>
<td>Wu (12)</td>
<td>11 to 16 Teeth</td>
<td>N = 9992</td>
<td>1.060</td>
<td>0.720</td>
</tr>
<tr>
<td></td>
<td>Joshipura (11)</td>
<td>17 to 24 Teeth</td>
<td>N = 44119</td>
<td>1.040</td>
<td>0.847</td>
</tr>
</tbody>
</table>

Number of teeth and relative risk of coronary artery disease.

### Figure 5

**Meta-Regression Analysis: The effect of Number of Teeth on the Log Risk Ratio of CHD**

Meta-regression analysis: the effect of the number of teeth on the log risk ratio of CHD.
Our meta-analysis of cohort studies indicated that there is 1.24 times increased risk (95% CI 1.14-1.36, \( P < .0001 \)) for CHD in the edentulous patients (<10 teeth). The results also indicated that an inverse relationship between the number of teeth and the RR of CHD may exist. Our attempt to evaluate this relationship resulted in trends toward supporting such a relationship without reaching statistical significance. Given the small number of point estimates that were available for this analysis, it is believed that the reason was the lack of statistical power rather than the lack of this association. Nonetheless, the impact of tooth loss on the incidence of CHD can be best evaluated with well-powered progressive studies. It is true that edentulous patients are less likely to adhere to oral hygiene such as brushing and flossing, which leads to severe periodontal disease. In addition, tooth loss is likely to reduce a person’s ability to masticate, leading to detrimental changes in food choices. Edentulous individuals tend to eat fewer amounts of fruits and vegetables and have high fat and carbohydrate content in their food.\(^{20,27}\) In addition, they tend to have more chances of having non-insulin-dependent DM\(^{28}\) and smoking\(^{29}\) habits as compared with normal dentate individuals, increasing the risk for CHD.

The mechanisms underlying this association between periodontal disease and CHD are not clearly understood. Spahr et al\(^{23}\) suggests that the periodontal pathogen burden, particularly \textit{Actinobacillus actinomycetemcomitans}, in the periodontal pockets may be a more important risk factor for CHD than clinical parameters assessing the severity of periodontal disease. This organism is present in human atherosclerotic plaque and can gain access to circulation through intact oral tissue.\(^{30}\) Lipopolysaccharide from this organism causes human macrophages to secrete cytokines (interleukins 1\(\alpha\) and 1\(\beta\) and tumor necrosis factor) that play an important role in atherothrombogenesis.\(^{31}\)

Studies have shown that elevated levels of cytokines, C-reactive protein, and fibrinogen are associated with periodontal disease. The atherothrombogenesis caused by these factors may suggest the possible link between periodontal disease and CHD. In addition, periodontal pathogens themselves can cause platelet aggregation and thromboembolic events by expressing platelet aggregation-associated protein.\(^{32}\)

The results of the current study are similar to the meta-analysis published earlier by Janket et al\(^{33}\) and Khader et al.\(^{34}\) The summary RR in Janket et al was 1.19 (95% CI 1.08-1.32). This risk estimate is more than the result of our meta-analysis. We considered all the studies included in the analysis by Janket et al,\(^{35}\) but some of them failed to qualify. Similarly, Khader et al\(^{34}\) found that overall adjusted risk for CHD is 1.15 times higher in the subjects with PD. However, this estimate includes both prospective studies and cross-sectional studies. In fact, Khader et al\(^{34}\) reported that the overall RR was reduced to 1.14 (95% CI 1.04-1.25) if the analysis was limited only to prospective studies. We have found similar result in the prospective study analysis. We did not perform combined analysis of prospective and cross-sectional studies.

**Limitations of the study**

We understand that the validity of our meta-analysis results depends upon the strength of association between periodontal disease and CHD shown in individual studies. Some of the studies show statistically significant association between these 2 variables, and some of the studies show statistically insignificant association. Including such studies in our meta-analysis increases the validity of the analysis and provides a more reasonable estimate of such an association. A careful interpretation of meta-analysis results is advised because it is based on the results of various observational studies that have different study designs and are prone to inherent biases. One of the major limitations of this analysis is that there exists great heterogeneity between estimation of periodontal disease. A standardized protocol for the assessment of periodontal disease is lacking. In addition, the presence of CHD is measured differently in different studies. Furthermore, although most of the studies have adjusted for the confounding factors, there could be potential biases due to inadequate confounding adjustment influencing the final result. For example, only few of the studies were adjusted for socioeconomic status of participants. This is an important confounding factor because we do not know if periodontal disease and edentulousness are more common in low-income groups who tend to have poor health outcomes. In addition, not much information was available about the dietary habits of participants.

Most of these studies did not provide detailed basic data that would allow us to compute the same type of risk estimate for each study. Including all of them would have increased the power of this study, but the results would not have been significantly different. Nevertheless, this meta-analysis provides a tool to understand and further strengthen the association between periodontal disease and CHD.

**Conclusions**

Our analysis suggests possible association between PD and CHD. Elevated levels of inflammatory mediators in patients with PD suggest their role in atherothrombogenesis leading to CHD. Future well-designed prospective cohort studies with uniform definitions of periodontal disease and CHD investigating the definite role of periodontal pathogen burden on the occurrence of CHD and management of patients with PD to reduce the future risk of development of CHD are necessary.
References