

# ORAL HEALTH, ATHEROSCLEROSIS, AND CARDIOVASCULAR DISEASE

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**ABSTRACT:** During the last two decades, there has been an increasing interest in the impact of oral health on atherosclerosis and subsequent cardiovascular disease (CVD). The advent of the inflammation paradigm in coronary pathogenesis stimulated research in chronic infections caused by a variety of micro-organisms—such as *Chlamydia pneumoniae*, *Helicobacter pylori*, and cytomegalovirus—as well as dental pathogens, since these chronic infections are thought to be involved in the etiopathogenesis of CVD by releasing cytokines and other pro-inflammatory mediators (e.g., C-reactive protein [CRP], tumor necrosis factor [TNF- $\alpha$ ]) that may initiate a cascade of biochemical reactions and cause endothelial damage and facilitate cholesterol plaque attachment. Yet, due to the multi-factorial nature of dental infection and CVD, confirming a causal association is difficult, and the published results are conflicting. The main deficit in the majority of these studies has been the inadequate control of numerous confounding factors, leading to an overestimation and the imprecise measurement of the predictor or overadjustment of the confounding variables, resulting in underestimation of the risks. A meta-analysis of prospective and retrospective follow-up studies has shown that periodontal disease may increase the risk of CVD by approximately 20% (95% confidence interval [CI], 1.08-1.32). Similarly, the reported risk ratio between periodontal disease and stroke is even stronger, varying from 2.85 (CI 1.78-4.56) to 1.74 (CI 1.08-2.81). The association between peripheral vascular disease and oral health parameters has been explored in only two studies, and the resultant relative risks among individuals with periodontitis were 1.41 (CI 1.12-1.77) and 2.27 (CI 1.32-3.90), respectively. Overall, it appears that periodontal disease may indeed contribute to the pathogenesis of cardiovascular disease, although the statistical effect size is small.

**Key words.** Oral health, periodontitis, atherosclerosis, coronary heart disease, stroke, peripheral vascular disease.

## (I) Introduction

Bacterial populations attached to tooth surfaces consist of biofilm communities sometimes 50-100 cells in thickness and with a bacterial density of up to  $10^{11}$  CFU/mg. Thus, the biofilm that colonizes tooth surfaces may be among the most complex that exist in nature. This is due, in part, to the non-shedding surface of the tooth, which allows for the development of persistent colonization and very complex ecosystems. There is a dynamic co-existence between commensal and pathogenic bacteria, which are protected from the natural physical and chemical antibacterial host defenses in these bacterial communities (Socransky *et al.*, 2002). Knowledge of the complex interactions between the resident microbial communities and the human host is of the utmost importance in our understanding of the development and pathogenesis of a variety of diseases, not just the typical infectious diseases. There is increasing evidence that oral infections may also play a role in the pathogenesis of many systemic diseases, and this may occur not only in ill and immunocompromised individuals, but also in those who are healthy (Meurman *et al.*, 1997).

In the late 1970s, experimental infection of germ-free chickens with an avian herpesvirus induced an arterial disease that resembled human atherosclerosis (Minick *et al.*, 1979). This finding initiated the 'systemic infection-heart disease' paradigm. In the late 1990s, this theory was further expanded by including the hyper-inflammatory response in the pathogenesis of cardiovascular disease (CVD). In this process, infections are able to cause indirect damage by releasing inflammatory mediators and elic-

ing different host-related reactions, such as monocyte hypersensitivity and different autoimmune responses. In fact, C-reactive protein (CRP) has emerged as a harbinger of future CVD (Ridker *et al.*, 1998). The paradigm that infection and inflammation may play a significant role in a variety of diseases that hitherto were thought to be caused by other pathogenic mechanisms has now drawn attention to the possible role of dental infections in the pathogenesis of chronic systemic diseases.

In the last ten years, several epidemiological studies have assessed the association between oral infection and systemic disease (for review, see Renvert, 2003). These studies have provided support that oral infections, specifically periodontitis, may confer independent risks for different systemic conditions (mortality, osteoporosis, diabetes mellitus, pulmonary infections, pre-term low-weight births, cardiovascular diseases, and infections in other body sites). Since cardiovascular diseases are the leading cause of death worldwide, greater attention has been focused on evidence that infections of the oral cavity might be associated with atherothrombosis: heart infarction, stroke, and peripheral vascular disease (Slavkin and Baum, 2000).

In animal experiments, *Streptococcus sanguis*, a predominant oral micro-organism, induces platelet aggregation, an important thrombotic process in arterial plaque formation (Herzberg *et al.*, 1992). Destructive periodontal disease, which involves Gram-negative bacteria, has been reported to be a significant predictor of coronary heart disease (Beck *et al.*, 1996). Because both coronary heart disease (CHD) and periodontal disease have a multi-factorial etiology, as well as a wide variety of possible confounding factors, a clear-cut consensus on the importance of the

relationship between these two conditions has been difficult to obtain. Some systematic reviews have highlighted the potential biases in the interpretation of data (Collins and MacMahon, 2001), and others have presented the mathematical analysis for the sources of disparities in the reported results (Janket *et al.*, 2003). In the present review, we will critically evaluate the data accumulated so far, and summarize the results. Because of the wide range of varied outcomes and predictors, a mathematical summary may not be feasible. However, strength of scientific evidence will be thoroughly examined according to the five Bradford Criteria for causality: temporal relationship, dose response, strength of the association, consistency, and biological plausibility (Hennekens and Buring, 1987).

## (II) Pathophysiology of Inflammation in Atherosclerosis

Inflammatory processes have become an integral part of the pathophysiology of atherosclerosis and are presumed to be involved from the initiation to the progression and final stages of infarction. Normal endothelium does not allow for the attachment of leukocytes. When initial damage of the endothelium occurs, either by infection or by an atherogenic diet, the endothelial cells express adhesion molecules that allow leukocytes to bind to them. These adhesion molecules are called 'vascular cell adhesion molecules' (VCAM) and 'intercellular adhesion molecules' (ICAM). Selectins and integrins also support leukocyte attachment (Libby *et al.*, 2002).

Once this attachment is established, the atheroma accumulates more lipids and promotes the production of various chemokines and growth factors that stimulate the recruitment of monocytes and macrophages. These chemokines also promote the migration of smooth-muscle cells. These muscle cells respond to the inflammatory stimuli by secreting specific enzymes (metalloproteinases) that are able to degrade elastin

and collagen. Further, these metalloproteinases may disintegrate the fibrous capsule holding the cholesterol plaque together, and cause plaque rupture. Plaque rupture greatly increases the risk of myocardial infarction and stroke.

During the past two decades, there has been an increasing interest in the role of chronic infections as risk factors for atherosclerosis (Ross, 1999; Leinonen and Saikku, 2000). In a recent meta-analysis, the odds ratio of chronic infection for early atherogenesis was 3.0 (Kiechl *et al.*, 2001). Intervention with roxithromycin for the treatment of *Chlamydia pneumoniae* among unstable angina patients (ischemic syndromes) decreased cardiac events (Gurfinkel *et al.*, 1997). However, a more recent study with the randomized controlled trial design, and with an acceptable follow-up time period, failed to show an effect of antibiotic treatment on the prevention of cardiac events (O'Connor *et al.*, 2003).

This relationship between chronic inflammation and atherogenesis has been recently expanded to include other pro-inflammatory processes related to a hyperactive immune response (Beck *et al.*, 1998) or autoimmune reaction to microbial or other metabolic stimuli. For example, systemic lupus erythematosus patients have been found to be at a higher risk for developing cardiovascular disease (Nuttall *et al.*, 2003). These generalized hyper-inflammatory states may be characterized by elevated CRP concentrations (Libby and Ridker, 1999; Mendall *et al.*, 2000).

## (III) Oral Infections and Coronary Heart Disease

Coronary heart disease (CHD) is the most important clinical manifestation of atherosclerosis. It is the single greatest cause of mortality in Western countries. For example, 33% of all annual deaths in the US are due to CHD. CHD afflicts 7 million Americans and is responsible for over 500,000 deaths annually (AHA, 2003). Mattila and colleagues were the first to show a statistical association between dental infections and advanced coronary atherosclerosis (Mattila *et al.*, 1989b). This original finding has been further investigated in many clinical and experimental studies.

Some study designs are better suited for the establishment of causal inferences between dental infections and CHD. The criteria needed to establish a causal association are presented in Table 1. We will begin with study designs that provide the weakest arguments for such an association and end with those that have the strongest evidence.

### (A) DESCRIPTIVE AND CROSS-SECTIONAL STUDIES

These types of studies are a useful tool for hypothesis generation. Usually, they are not adjusted for all major co-existing risk factors (confounders), and since the outcome (CHD) and the predictor (oral disease) are measured at the same time, a temporal relationship cannot be established. Thus, the strength of evidence for the causal association

**TABLE 1**  
**Bradford Criteria for Establishment of Causal Association**

	Interpretation	Comments
Temporal relation	Does the predictor occur before the outcome?	This criterion must be satisfied at all times.
Dose response	Do severe predictors cause more severe outcomes?	This does not always hold true. Some causal relations occur at a threshold and, above and below, have different responses: disease or no disease.
Strength of association	Is the rate of disease high in the exposed vs. unexposed?	Some risk factors generate very high risk ratio ( <i>i.e.</i> , smoking). However, most dental research deals with very weak predictors.
Consistency	Does research in different countries, with different groups or institutions, generate similar results?	Due to research methods, clinical or epidemiologic, or degree of confounding adjustment, results may not be consistent, especially if the predictor is weak and confounders are strong. Special attention must be paid to illicit 'true association'.
Biological plausibility	Does it make biological sense?	Etiopathogenesis is important in this criterion. Do we have a strong biological reason to believe there is a link? This should always hold true.

Adapted from Hennekens and Buring (1987).

is weak. Examples of this category include the study by Paunio *et al.* (1993), who reported that missing teeth were associated with ischemic heart disease, and the study by Syrjänen and co-workers, who reported that dental infection was associated with cerebral infarction in young and middle-aged men (Syrjänen *et al.*, 1989). We have also observed that oral health was poor in coronary heart disease patients in comparison with non-CHD patients (Meurman *et al.*, 2003a). These studies did not adjust for all pertinent risk factors, and there might be residual bias in these reports. Nevertheless, the findings were consistent and interesting enough to warrant further research in the area.

Loesche *et al.* (1998) published a study in which the confounding variables were well-controlled, and the results seemed to suggest a positive association between dental disease and cerebrovascular accidents in US veterans. However, this study was cross-sectional, and causal inferences could not be made.

In Sweden, Buhlin and co-workers have published a national questionnaire study in which a significant association was observed between self-reported bleeding gums and CVD (OR 1.60; CI 1.19-2.15) and between the presence of dentures and CVD (OR 1.57; CI 1.13-2.20). The data analysis was adjusted for age, smoking, income level, socio-economic and marital status, and education (Buhlin *et al.*, 2002). The same group also reported results from another questionnaire which suggested that the risk of CVD was increased if the patient had experienced problems with his/her teeth in the absence of dental care (OR 2.45; CI 1.066-5.625). Here, the odds ratio for the association of self-reported bleeding gums and CVD was 3.07 (CI 1.288-7.313) (Buhlin *et al.*, 2003a). The logistic regression model was adjusted for age, gender, smoking, diabetes, socio-economic and marital status, and education. We question the reliability of data based on questionnaires rather than clinical findings, and, consequently, a causal inference cannot be made because of the study design.

## (B) CASE-CONTROL STUDIES

Case-control studies generate the next level of strength of evidence, although they are still laden with biases. A true case-control study requires that (1) the disease be ascertained at the beginning of the study, and (2) that the past exposure, according to the disease status, has been assessed. For example, it must be ascertained that CHD patients and controls are similar in every aspect except the CHD status. The status of their past oral health must be documented for several years or decades, and this time period should match the induction period of CHD (see below).

Mattila *et al.* (1989b) investigated dental infection and acute myocardial infarction (AMI) and published an early trend-setting paper in this field of research. They combined several dental infections and created a Total Dental Index (TDI). The TDI was significantly associated with AMI after adjustment for age, social class, smoking, serum lipid concentrations, and the presence of diabetes. However, the study was a case-control study, which is prone to selection bias, and, consequently, the results might also be biased (Mattila *et al.*, 1989b). To resolve this shortcoming in study design, Mattila *et al.* (1995) undertook a similar study in a longitudinal format, which will be discussed in their 'prospective cohort study' (see below).

In another case-control study, the Finnish group also examined the relation of age, dental infections, and coronary heart disease in elderly patients (Mattila *et al.*, 2000). The conceptual basis of this study might be flawed, because the number of missing teeth increases as one ages, which, in turn, may lower the dental infection potential; but missing teeth may also signi-

fy possible past dental infection and impaired chewing ability, which, in turn, may increase the risk of atherosclerosis *via* an unfavorable dietary intake. Thus, these opposing factors might have negated each other's effects, which could explain the null results (for further comments, see Janket *et al.*, 2001).

We have further improved the TDI formulated by Mattila and co-workers in our case-control study by developing a mathematical scoring system called the Asymptotic Dental Score (ADS; Janket *et al.*, 2004). The ADS is a mathematically proper way to combine several oral health factors, and the likelihood ratios of these factors reflect their relative importance. ADS has significantly facilitated the interpretation of several regression models, above and beyond CRP, HDL, and fibrinogen, all proven predictors of CVD. This suggests that oral health has the potential to affect systemic health *via* more than just the inflammatory process (Janket *et al.*, 2004).

Rutger Persson and colleagues (2003), in a well-conducted study in Sweden, studied the association of the severity of periodontal disease with clinically confirmed AMI in 80 patients and 80 matched control subjects. This group calculated odds ratios (OR) for AMI and periodontal disease based on four different radiographic cut-off points for the extent of alveolar bone loss. The results showed greatest OR if bone loss exceeded 4 mm around 50% of the teeth (OR 14.1, CI 5.5-28.2). The authors concluded that the study was particularly designed to evaluate the relationship between a clearly defined serious cardiovascular event and periodontitis, and that the risk for CVD was indeed elevated with increasing severity of periodontal disease. They therefore suggested that dentists have the responsibility to identify patients at risk for CVD (Rutger Persson *et al.*, 2003). We believe, however, that data for such a strong recommendation are still sparse. Nevertheless, we agree with Mattila (2003), the original presenter of the hypothesis linking dental infection and CVD, that the measurement of alveolar bone loss as recommended by Rutger Persson *et al.* (2003) might be the best way to assess the severity of periodontal disease in large studies, because the radiographic assessment can be done in a blinded fashion, and several independent researchers can be used.

## (C) LONGITUDINAL STUDIES

This study design establishes the temporal relation between a predictor and an outcome. Thus, causal association may be established if the proper confounding factors are adjusted. A comparison of the incidences of CHD in the groups with and without dental infection may allow one to estimate the impact of dental infection on CHD. As in most observational studies, other risk factors have to be adjusted mathematically.

In 1993, DeStefano and colleagues examined the relation between periodontal disease and CHD and observed an approximately 25% increased risk for CHD (RR 1.25, CI 1.06-1.48) in individuals with periodontal disease after controlling for race, education, systolic blood pressure, cholesterol, alcohol consumption, Body Mass Index (BMI), exercise, and poverty index. This was the first large-scale study, with a follow-up period of 14 years, and one that adjusted reasonably well for confounding factors. These investigators used population-based data obtained from The National Health and Nutrition Epidemiologic Survey (NHANES I). Although some data on smoking were missing, the results appeared to reflect the smoking habits of the general population fairly closely.

Mattila and colleagues (1995) also carried out a small prospective cohort study in which the TDI (a combination of

several oral infections) was significantly associated with CVD after adjustment for other established CVD risk factors. However, the follow-up length of 7.2 years was marginally inadequate, as compared with the postulated induction period of CHD, which is approximately 10 years (Danesh *et al.*, 1997), and the sample size was too small. Nevertheless, the authors observed about a 21% (CI 1.08-1.36) increase in the risk for developing CVD in individuals with high TDI when compared with those with lower TDI. This finding was similar to that previously discussed in the case-control study section.

Beck *et al.* (1996) reported that periodontal pocket depth and alveolar bone loss were significantly associated with CHD and stroke among US veterans. They reported a relative risk of 1.49 (CI 1.07-2.15), although this study has been criticized for not vigorously controlling for the strongest confounder, smoking. We have examined their baseline smoking data and found that the proportions of smokers were equal in both the CHD and the non-CHD groups. Thus, the impact of not accounting for the smoking confounder was probably not significant. However, these results are based on data from veterans who have a higher morbidity than the general US population, and therefore the results may not be applicable to the US population in general.

Concurrently with the study by Beck *et al.*, Joshipura and colleagues (1996) reported that poor oral health did not increase the risk of fatal and non-fatal myocardial infarction (MI) among health professionals. This was a well-conducted, large-scale epidemiologic study, but there are several points to consider when interpreting the results. The length of the follow-up was only 6 years, which is shorter than the presumed induction period for CVD as determined by Danesh *et al.* (1997). Further, the periodontal status was measured by a self-reported questionnaire. This imprecise predictor assessment might have attenuated the relative risks and contributed to the 'null result'. The obtained relative risk was 1.04 (CI 0.86-1.25). When a more precise predictor, the number of teeth, was used in the statistical analyses, the authors observed a significant association between the number of teeth and MI.

Genco *et al.* (1997) studied the relationship, among Native Americans, between tooth loss and alveolar bone loss and CVD as confirmed by electrocardiogram (ECG). They observed a high relative risk of 2.69 for CVD with alveolar bone loss (Genco *et al.*, 1997). However, Native Americans have a much higher rate of incidence of diabetes and CVD relative to the general US population. Moreover, the high prevalence of CVD in this cohort, the fact that the predictor was tooth loss, which tends to be a stronger predictor than pocket depth or periodontitis, and the fact that the authors did not adjust for smoking might have biased the results in favor of an association between tooth loss and CVD.

Morrison *et al.* (1999) compared fatal CHD incidences among individuals with gingivitis, severe gingivitis, and periodontal pockets and with those in control patients with no periodontitis. The authors observed an almost two-fold increase in CHD events after 21 years of follow-up among the patients with periodontitis (Morrison *et al.*, 1999). This study was a retrospective follow-up study and, as such, is prone to information bias, since the outcomes had already occurred. This, in turn, might have caused an overestimation of the relative risk.

Hujoel and colleagues (2000) examined the association of fatal and non-fatal CHD in individuals with gingivitis and periodontitis as compared with that in individuals without periodontal disease. They observed a non-significant increase

(14%) in risk for CHD in patients with periodontitis (RR 1.14, CI 0.96-1.36) (Hujoel *et al.*, 2000). This group of investigators analyzed the NHANES data, as was also done by DeStefano's group (1993). However, these two groups reported contradictory results. The disparity appears to have originated from the degree of adjustment carried out with the covariates. In our opinion, the adjustment of confounding was excessive in the study by Hujoel and co-workers. The covariates in question were established CHD risk factors, but we are not certain whether all these variables are true confounders. To be a confounder, a variable has to be causally linked to the outcome and also causally associated with the predictor. For example, smoking is causally associated with periodontal disease but also with CHD. Therefore, rigorous adjustment for smoking is necessary for estimation of the unbiased effect of periodontal disease on CHD. Furthermore, are BMI, exercise, and family history of heart disease confounders? We know that these factors are causally associated with heart disease, but do we know if these variables are causally associated with periodontal disease? If not, then the variables may not be true confounders. Saito *et al.* (1998) published a letter in the *New England Journal of Medicine* which stated that subjects with high BMI tend to exhibit poor periodontal status. However, this study did not provide a causal relation between BMI and periodontal disease.

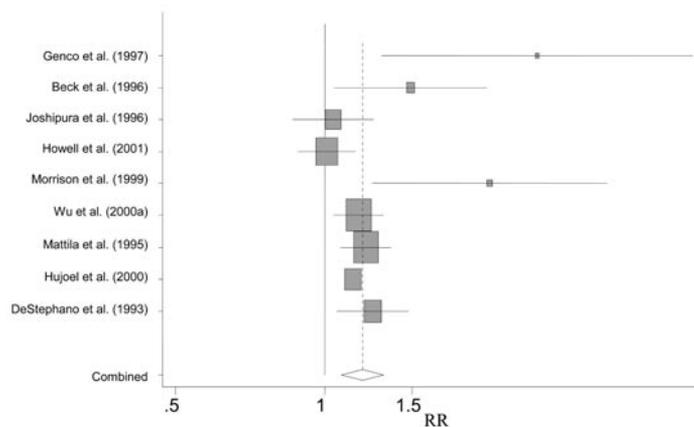
The epidemiological study by Howell *et al.* (2001) was also unable to report a significant association between CVD incidence and periodontal disease (RR 1.20, CI 0.76-1.89). In this study, confounding variables were very reasonably controlled, and the follow-up length was adequate (12.5 years). However, they determined the presence/absence of periodontal disease by means of a questionnaire, and fatal stroke was not included in the analyses. These two factors, in addition to the fact that all the participants were physicians and their disease experience may be different from that of the general population, might have contributed to a null relation found in the study.

From the results of these nine cohort studies, where the exposure, *i.e.*, periodontal disease, occurred some time before the outcome, *i.e.*, incidence of CVD, the association may be interpreted as causal, if reasonable adjustment for confounding factors was accomplished. Our group has recently reviewed these nine longitudinal datasets that satisfied our inclusion criteria (Table 2, Fig. 1) (Janket *et al.*, 2003). We found that periodontal disease had a stronger effect on fatal CHD and stroke than on non-fatal or fatal and non-fatal CHD combined. We quantified the increased risk of CVD due to periodontal disease by weighted average and found that the increase in risk due to periodontal disease appeared to be approximately 20% (RR 1.19, CI 1.10-1.38). As we have discussed above, some studies might represent a group with a higher or lower disease experience than the general US population. Consequently, combining these overestimations and underestimations might therefore have provided reasonably unbiased results.

Recently, Tuominen and colleagues (2003) reported that oral health was not a significant predictor of a fatal CHD after the proper adjustment for confounding factors. They concluded that the association between oral health and fatal CHD might simply be due to behavioral factors. They followed 6527 patients for 12 years and documented 319 CHD deaths. However, the data were analyzed by proportional hazard regression, where the sample size constituted the number of events and not the total number ( $n = 6527$ ) of participants. Thus, this study appears to be very under-powered. To observe about a 30% increase in the risk for

coronary heart disease because of periodontal disease, one would need at least 1265 or more events (CHD deaths) (Hujoel *et al.*, 2000). Thus, we cannot be certain if the reported null result was due to a true 'no relationship' or simply due to the absence of enough statistical power to bring out the difference.

Scannapieco *et al.* (2003) have recently also reviewed existing data on the association between periodontal disease and the risk for atherosclerosis and its clinical manifestations. Their review was completed by a consensus report critically examining the strength of evidence presented. It should be emphasized that there are no data from randomized controlled interventional trials. The published data are merely from observational studies. We thus agree with the summary statement of Scannapieco and colleagues and the consensus report (2003) that there is insufficient evidence available to justify periodontal intervention to prevent the onset or progression of atherosclerosis-induced diseases. These authors also duly pointed out that there is great heterogeneity between the studies in the assessment of oral or periodontal disease. Consequently, there is a need for a broadly accepted and standardized protocol for such an assessment in future studies (see also the comment



**Figure 1.** Summary relative risk of periodontal disease and coronary heart disease. Reproduced with permission (Janket *et al.*, 2003).

above at the end of the previous subsection).

**TABLE 2**  
**Description of Studies<sup>b</sup> Included in Meta-analyses**

Authors	Study Type/ Quality (score <sup>a</sup> )	Length of Follow-up	Sample Size/ # of Cases	Relative Risk (Confidence Interval)	Age Category	Outcome Measurements	Predictor Measurements	Confounders Adjusted
Beck <i>et al.</i> (1996)	Prospective cohort*	18 yrs	1147/207	1.49 (1.07-2.15)	21-80	Fatal MI, non-fatal MI, stroke (defined by ICD-9 code 410-414)	By probing pocket depth, alveolar bone loss	Diabetes, BMI, SBP, cholesterol
DeStefano <i>et al.</i> (1993)	Prospective cohort***	14 yrs	9760/1425	1.25 (1.06-1.48)	25-75	Mortality d/t CHD, Admission d/t CHD (defined by ICD-9 code 410-414)	Gingivitis, mild periodontitis, moderate periodontitis, severe periodontitis	Race, education, SBP, cholesterol, diabetes, alcohol, smoking, BMI, exercise, poverty
Genco <i>et al.</i> (1997)	Prospective cohort*	10 yrs	1372/68	2.68 (1.30-5.50)	< 60	CVD by ECG	Tooth loss, alveolar bone loss	Diabetes, cholesterol, hypertension
Howell <i>et al.</i> (2001)	Prospective cohort**	12.5 yrs	22,037/2042	1.01 (0.86-1.15)	40-84	Death due to CVD, non-fatal MI, non-fatal stroke	History of periodontitis	Diabetes, hypertension, BMI, smoking, exercise, alcohol use
Hujoel <i>et al.</i> (2000)	Prospective cohort***	8-10 yrs	8032/1265	1.14 (0.96-1.36)	25-74	First hospitalization, re-vascularization, death due to CHD	No periodontitis, gingivitis, periodontitis	Race, education, poverty, marital status, SBP, DBP, total cholesterol, diabetes, exercise, BMI, alcohol use, smoking, nervous breakdown
Joshipura <i>et al.</i> (1996)	Prospective cohort*	6 yrs	44,119/757	1.04 (0.86-1.25)	40-75	Fatal MI, non-fatal MI	Questionnaire/History of periodontitis	Smoking, BMI, dietary habits, exercise, family MI Hx
Mattila <i>et al.</i> (1995)	Prospective cohort***	7.2 yrs	214/52	1.21 (1.08-1.36)	< 60 (male), < 65 (female)	Death due to CVD, admission due to CVD	Total Dental Index, including periodontitis, periapical lesion, dental caries, pericoronitis	Diabetes, BMI, hypertension, smoking, cholesterol, triglyceride, socio-economic status
Morrison <i>et al.</i> (1999)	Retrospective cohort**	21 yrs	10,368/416	2.15 (1.25-3.72)	35-84	Fatal CHD	No periodontitis, mild gingivitis, severe gingivitis, periodontal pocket	Cholesterol, smoking, diabetes, hypertension, residence
Wu <i>et al.</i> (2000a)	Prospective cohort***	10+ yrs	9962/803	1.17 (1.04 - 1.31)	25-74	Fatal and non-fatal strokes (including hemorrhagic, non-hemorrhagic, and transient ischemic events)	No periodontal disease, gingivitis, gingivitis with pocket, advanced periodontitis	Race, education, poverty index, smoking, diabetes, hypertension, alcohol use, cholesterol, BMI

<sup>a</sup> Quality score: \*45-59% of maximum score achieved, \*\*60-79% of maximum score achieved, and \*\*\*80-90% of maximum score achieved.

<sup>b</sup> All studies adjusted for age and gender. Reproduced with permission (Janket *et al.*, 2003).

#### (IV) Oral Health and Biomarkers of Cardiovascular Disease

Several studies have examined periodontal disease or other oral health parameters in relation to intermediate variables or biomarkers of CVD. One such example is the finding by Kweider *et al.* (1993) that severe gingivitis was associated with a higher leukocyte count and serum fibrinogen level. Wu and colleagues (2000b) reported that increased serum levels of CRP and fibrinogen, both well-established biological markers for CHD, were associated with periodontitis, while Mattila and colleagues (1989a) reported that dental infection was significantly associated with increased von Willebrand factor antigen. In this context, it is interesting to point out that a stronger association has been observed between gingivitis and CVD than between periodontitis and CVD (Morrison *et al.*, 1999; Meurman *et al.*, 2003b).

Slade and colleagues (2000) analyzed the Third National Health and Nutrition Examination Survey (NHANES III) data to ascertain the acute-phase inflammatory response to periodontal disease, as measured by CRP, in the US population. Their findings were inconclusive, because both periodontitis and edentulism were associated with increased CRP. However, part of the problem was due to the high threshold that was set for CRP to be 'elevated'. The threshold level of 10 mg/L set in 1996 was too high to detect any meaningful differences between the groups. Today, the threshold level is considered to be near 3 mg/L, because the much more accurate and high-sensitivity immunoturbidometry or immunonephelometry methods permit the measurement of much lower levels of CRP.

Hasegawa *et al.* (2002) found that, among smokers, the total white blood cell count (WBC) was associated with age, periodontal disease, BMI, triglycerides, and high-density lipoprotein cholesterol (HDL); while among non-smokers, blood pressure was a significant factor for elevated WBC, whereas triglyceride was not. They were unable to separate the effects of smoking from those of periodontitis on WBC count, although they provided a reference WBC of  $4.96 \pm 10^9$  for a non-smoker without periodontal disease. In our opinion, WBC is an overly broad marker, and thus the utility of this measure may be limited unless other corroborating data are presented.

Noack *et al.* (2001) observed statistically significant increases in CRP levels in 109 subjects with moderate to severe periodontitis when compared with 65 periodontally healthy controls ( $P = 0.036$ ). After adjustment for factors known to be associated with elevated CRP, including age, smoking, BMI, triglycerides, and cholesterol, subjects with high levels of mean clinical attachment loss had significantly higher mean CRP levels ( $4.06 \pm 5.55$  mg/L) than did controls ( $1.70 \pm 1.91$  mg/L,  $P = 0.011$ ). The presence of periodontal pathogens—including *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Tanerella forsythensis*—from subgingival plaque samples was positively associated with elevated CRP levels ( $P = 0.029$ ). CRP levels were also reported to be higher in 50 CVD patients with severe periodontitis (> 4-mm-deep gingival pockets) than in 46 healthy cases (Buhlin *et al.*, 2003b). We have also recently reported that both CRP and serum fibrinogen concentrations were significantly higher in CVD patients ( $n = 256$ ) than in controls ( $n = 250$ ) (Meurman *et al.*, 2003b). The calculated oral infection sum score, 'modified dental index' (which is the arithmetic sum of x-ray findings on periapical, pericoronal, and furcation lesions, deep periodontal pockets, jaw cysts, retained roots, and tertiary caries), was associated with high values of these inflammatory

markers in the patient group (*e.g.*, odds ratio for higher-than-median fibrinogen concentration was 1.21 [CI 1.01-1.23]).

Takata and colleagues (2001) studied the impact of tooth loss on coronary heart disease among octogenarians. In a group of older Japanese, the presence of fewer than 20 teeth was associated with abnormal electrocardiogram (ECG) findings. The authors controlled for other independent CHD risk factors, including gender, smoking, serum cholesterol, glucose, blood pressure, and BMI. The authors concluded that tooth loss may be an independent predictor of abnormal ECG findings.

Katz *et al.* (2002) were the first to report the relation between hypercholesterolemia and severe periodontitis. They observed that higher cholesterol levels coincided with higher scores on the Community Periodontal Index of Treatment Needs (CPITN). The authors did claim that stepwise adjustments of other confounding variables were made, but we are skeptical of the appropriateness of their method. In addition, the study was cross-sectional, and no causal inference could be derived from their results.

In the study by Buhlin's group (2003b), a relationship was found between periodontitis and low concentrations of HDL. BMI was also higher in the CVD patients with periodontitis than in healthy controls (mean BMI was 25.7 *vs.* 24.1, respectively;  $p < 0.05$ ). The analyses were adjusted for age, gender, and smoking. These findings support the earlier results of Katz *et al.* (2002) indicating that periodontal disease may also influence blood lipid concentrations.

Joshipura *et al.* (2004) have recently published cross-sectional data from the prospective male health professionals follow-up study, where self-reported periodontal disease was analyzed in a sample of 468 men with respect to a variety of biomarkers of CVD. Their results showed, in part, that periodontal disease was associated with higher levels of CRP and LDL, thereby supporting the hypothesis that periodontal disease might also be causally linked with CVD.

Beck *et al.* (2001) examined the association, if any, between periodontitis and carotid artery intima-media wall thickness (IMT), an indication of subclinical atherosclerosis. Utilizing cross-sectional data from the Atherosclerosis Risk in Communities (ARIC) Study from 1996 to 1998, they observed an approximately 30% increase in risk of having  $IMT \geq 1$  mm in individuals with severe periodontitis (OR 1.31, CI 1.03-1.66). The study was adjusted for race, research site, and diabetes.

Ajwani and colleagues (2003) attempted to determine if edentulism and dentate status with or without periodontal disease were linked to mortality. They found that mortality from all causes was non-significantly associated with edentulism and dentate status. However, among the dentate with periodontal disease, CVD mortality was significantly increased (RR 1.97, CI 1.01-3.85). The authors further concluded that mucosal inflammation in edentulous subjects might have contributed to CRP elevation. This was a 10-year follow-up study, but the sample size might have been too small for the observation of a significant relation between oral health and mortality from all causes.

Recently, Iwamoto and colleagues (2003) reported that, in 15 patients with chronic periodontitis, topical application of 10 mg of minocycline into periodontal pockets for one month caused a significant decrease in CRP and TNF- $\alpha$  levels (Iwamoto *et al.*, 2003). The mean CRP values decreased from  $1.6 \pm 1.7$  ng/mL to  $0.93 \pm 1.0$  ng/mL ( $p < 0.01$ ). To our knowledge, this is the first intervention study where locally delivered antimicrobial treatment of periodontal disease was shown to affect CVD risk biomarkers.

However, the number of patients in this study was too low to warrant any firm conclusions, and the authors did not adjust for BMI, which was a major determinant of CRP in their statistical model. However, since they used the baseline values before treatment as controls, the BMI change might have had a negligible impact on the results during the one-month study period.

In summary, even though gingivitis and periodontal disease have been shown to exert systemic effects, the evidence is not sufficiently strong to indicate a cause-and-effect relationship. More studies are needed to establish the role of these and other oral diseases in generating or modifying the host factors that play a role in the pathogenesis of atherosclerosis.

### **(V) Oral Health and Other Cardiovascular-disease-related Parameters**

Emingil and colleagues (2000) investigated whether poor periodontal condition was associated with an acute episode of myocardial infarction (AMI) among chronic coronary heart disease patients. They compared the probing pocket depth (PPD) and bleeding on probing (BOP) of 60 cardiac patients with AMI and 60 patients without AMI. The proportion of patients with BOP and PPD  $\geq 4$  mm was significantly associated with AMI. However, they did not report any adjustment of confounding factors.

Malthaner *et al.* (2002) examined the relation between periodontal disease and asymptomatic coronary heart disease (CAD) where there was 50% stenosis in at least one of the epicardial arteries. Those without periodontal disease had less than 50% stenosis in these arteries. After adjustment for age and smoking history, the association of CAD and periodontal disease was not statistically significant. The odds ratio for attachment loss was 1.06, and that for pocket depth  $\geq 6$  mm and for bone loss, 1.31 ( $p = 0.21$ ). In our previous review, we observed that, with the more severe cases, such as fatal AMI, the association between cardiac disease and periodontal disease was stronger (Janket *et al.*, 2003). Our findings are in contrast to those of Malthaner *et al.* (2002), and the contradictory findings could be due to the fact that, in the latter study, the patients presented with asymptomatic CHD.

In a small case-control study (35 cases and 51 controls), Lopez *et al.* (2002) examined the relationship between oral health parameters and CHD and found that mean attachment loss was significantly associated with CHD status (OR 3.17, CI 1.31-7.65). Similarly, the mean pocket depth was also positively associated with CHD (OR 8.64, CI 1.22-61.20). The number of teeth was not significantly different between the groups, and we presumed that this was due to the fairly young age of the cohort (from 30 to 50 years old). In spite of the high prevalence of periodontal disease in this population (almost 100%), the sample size was small, and this is reflected in the large confidence intervals. Nevertheless, the authors did control for the minimal necessary variables and drew reasonable conclusions. However, no causal inferences can be made from their results, due to the study design.

Angeli and colleagues (2003) observed that the left ventricular mass increase in heart muscle, as evaluated by echocardiogram, was significantly associated with periodontal status, as measured by the CPITN. The authors provided the following potential mechanism for this association:

- (a) Both hypertrophic heart and periodontium may share microcirculatory dysfunction and arteriolar and capillary rarefaction (Chapple *et al.*, 2000; Serne *et al.*, 2001).
- (b) Pressure overload may induce left ventricular hypertrophy and generalized narrowing of the luminal diameter

of micro-vessels, resulting in vascular rarefaction. This may lead to ischemia in cardiac and periodontal tissues.

As the authors admitted, the above pathobiology may resemble the effects of diabetes, but this study did not adjust for diabetes. However, some investigators consider type 2 diabetes as an intermediate stage in the causal pathway leading to CHD (Grundy *et al.*, 2002). Therefore, there might not be a need to control for diabetes. Angeli and colleagues (2003) further suggested that periodontal disease can provide an easily accessible biological assay for a more accurate definition of cardiovascular risk profile in an individual subject, a suggestion that has also been made by our group as a result of our data analyses (Janket *et al.*, 2004).

Desvarieux and colleagues (2003) attempted to determine if periodontal disease, tooth loss, and carotid artery plaque could be possible precursors of stroke and CHD. In a cross-sectional study of 711 participants, they observed a significant relation between subclinical atherosclerosis and tooth loss after adjustment for conventional CVD risk factors (Desvarieux *et al.*, 2003). They concurred with our opinion that many socio-economic factors overlapped but were not exactly identical. Thus, adjustment for several socio-economic factors could lead to an over-adjustment and may attenuate the relation between the CVD and oral health (Janket *et al.*, 2001).

Lowe *et al.* (2003) also observed that total tooth loss was significantly associated with CVD after adjustment of age, sex, smoking, social class, and citrus fruit consumption (RR 1.50, CI 1.12-2.25,  $p = 0.02$ ). However, this was a cross-sectional study, and a causal inference cannot be made.

To sum up, we conclude here that data are still sparse regarding the effect of oral health on cardiovascular-disease-related parameters. More studies with larger patient population groups are needed.

### **(VI) Studies on Oral Pathogens and Related Factors**

In addition to the earlier findings by Herzberg and colleagues (1992), several studies have reported a direct link between oral pathogens and atheroma. Chiu (1999) isolated *P. gingivalis* and *S. sanguis* in the arterial plaque from a carotid endarterectomy specimen that suggested possible invasion of the odontopathogens in the carotid atheroma. Dorn and colleagues (1999) reported that *P. gingivalis* appeared to invade coronary artery endothelial cells and increase the degradation of endothelial cell proteins. Haraszthy and colleagues (2000), using specific oligonucleotide primers in polymerase chain reaction (PCR) assays, detected microbial ribosomal RNA in atheroma plaque. The micro-organisms tested were *C. pneumoniae* as well as dental pathogens and cytomegalovirus. Thirty percent of the surgical specimens were positive for *T. forsythensis*, 26% for *P. gingivalis*, 18% for *A. actinomycetemcomitans*, and 14% for *P. intermedia* (Haraszthy *et al.*, 2000).

A genetic propensity for hyper-responsiveness to inflammatory stimuli may be one of the mechanisms that explain how periodontal disease might be associated with CVD. Kornman's group reported that certain genetic markers for IL-1A and IL-1B were associated with periodontitis but not with atherosclerosis, while IL-1B and IL-1RN were associated with atherosclerotic plaque but not with periodontitis (Kornman *et al.*, 2002). They suggested that there might be a genetically determined inflammatory hyper-response underlying both of these pathologic states. However, this issue has not yet been unequivocally resolved.

Another mechanism postulated by Beck and colleagues (1999) and Di Napoli *et al.* (2001) is that monocytes might be

hyper-responsive to bacterial antigens, a phenomenon which might also be genetically determined. This hyper-responsive propensity had been postulated to contribute to elevated CRP levels subsequent to an infection or other pro-inflammatory stimuli. In their report, Di Napoli *et al.* (2001) illustrated that the pattern of CRP changes was significantly associated with mortality after an ischemic stroke. Furthermore, they were of the opinion that periodontal disease could stimulate the production of CRP.

Choi and colleagues (2002) isolated *P. gingivalis* heat-shock protein-specific T-cells in atherosclerotic plaque from subjects with severe atherosclerosis. Bacterial heat-shock proteins are believed to be involved in regulating autoimmune mechanisms, and they also appear to be associated with the pathogenesis of periodontitis (Choi *et al.*, 2004).

Taylor-Robinson and colleagues (2002) isolated several infectious agents by DNA identification methods from all major arteries affected by atherosclerosis. Among these were *A. actinomycetemcomitans* and *P. intermedia*, in addition to *C. pneumoniae*. Nearly 40% of specimens were positive for *C. pneumoniae* DNA, and 35.4% were positive for a mixture of *Chlamydia* and oro-dental pathogen DNA. These findings suggest a possible invasion of the major arteries by oro-dental pathogens together with *Chlamydia*. Interestingly, Mäntylä *et al.* (2004) have recently shown that traces of *Chlamydia* can also be detected in periodontal pocket samples.

Taniguchi *et al.* (2003) examined the relation of carotid artery stenosis and *P. gingivalis* immunoglobulin G levels among non-obese diabetic patients without overt CVD. They observed that mean IMT in the arterial plaque-free area was not significantly different but that the degree of stenosis in the plaque segments was significantly higher in individuals with a higher IgG titer to *P. gingivalis* vs. a lower titer ( $12.0 \pm 2.2\%$  vs.  $5.5 \pm 1.4\%$ ,  $p = 0.009$ ). These results suggest that *P. gingivalis* affects the plaque area of an artery and that the influence of *P. gingivalis* is initiated well before the manifestation of symptoms of CVD.

We conclude here that data published from the studies on oral pathogens and other related factors are still insufficient for the assessment of the role of periodontal micro-organisms in the initiation and/or development of atherosclerosis, although the available evidence is very intriguing and warrants further research.

### (VII) Oral Health and Stroke

Cerebrovascular ischemic stroke is second in importance after CHD regarding the clinical manifestations of atherosclerosis. The annual incidence is approximately 10/100,000 patients with atherosclerosis in the US and in many European countries. Stroke remains the third leading cause of death (after CHD and cancer) in developed countries (Pulsinelli, 1996). Similar to CHD, poor dental health was found to be statistically associated with stroke. Syrjänen *et al.* (1989) observed that the signs of dental infections were more prevalent in men with ischemic stroke than in controls. However, in the same case-control study, the most significant association between dental infection and stroke was seen in cases with a preceding febrile infection, where the RR was 9 (CI 2.2-80). Similar findings were reported later by Grau *et al.* (1995) in a larger patient population of 197 patients and 197 random controls matched for age, sex, and area of residence. Here, the OR of a preceding infection to increase the risk for stroke was 4.5 (CI 2.1-9.7). However, these were cross-sectional studies, and not all independent confounding factors were adjusted.

Beck and colleagues (1996) did not separate hemorrhagic

stroke from ischemic stroke but observed a very strong association of periodontitis with the incidence of stroke among US veterans (RR 2.8, CI 1.45-5.48). The veterans are known to have higher disease experience of stroke, but combining hemorrhagic stroke and ischemic stroke might have underestimated the true impact of periodontal disease. Thus, this result may not be as biased as it appears.

Morrison *et al.* (1999) observed a non-significant increase in risk of fatal stroke in periodontitis patients (RR 1.63, 95% CI 0.72-3.67). Wu and colleagues (2000a), also utilizing the aforementioned NHANES data, examined the relationship between periodontal status and fatal and non-fatal stroke. They found an approximately 17% increase in the risk for stroke among those with severe periodontal disease in comparison with periodontally healthy individuals (RR 1.17, CI 1.04-1.31). When the analysis was restricted to fatal stroke, however, the result was remarkably similar to that in the report from Beck and co-workers (RR 2.90, CI 1.49-5.62), even though these studies were conducted in two different cohorts (Wu *et al.*, 2000a).

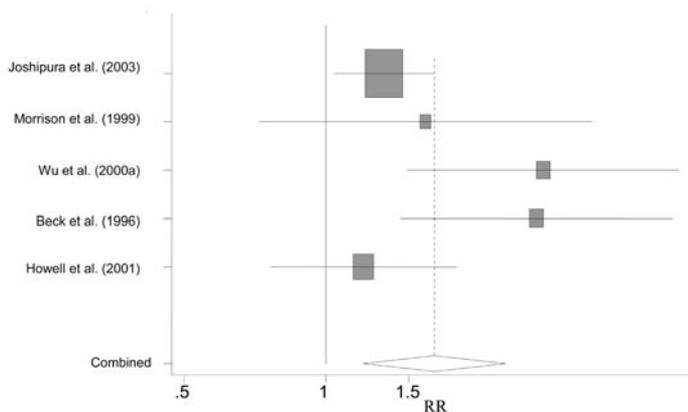
Joshi *et al.* (2003) recently reported a significant association between stroke and periodontitis (RR 1.33, CI 1.03-1.70) and between stroke and number ( $n = 16$ ) of teeth (RR 1.74, CI 1.08-2.81). In our previous review, we observed the relationship between periodontal disease and stroke to be much stronger than that between periodontal disease and CHD (Janke *et al.*, 2003). Earlier on, we stated that, depending on the parameter used to assess periodontal disease, there might be a need for a statistical correction to compensate for the possible error caused by the selected parameter, which may or may not adequately take into account the severity of the disease. Fig. 2 shows a summary of the studies that have focused on the risk of stroke due to periodontal disease. Due to the heavier statistical power of the large epidemiologic studies, the final summary RR may be underestimating the true relationship between stroke and periodontal disease.

### (VIII) Oral Health and Peripheral Vascular Disease

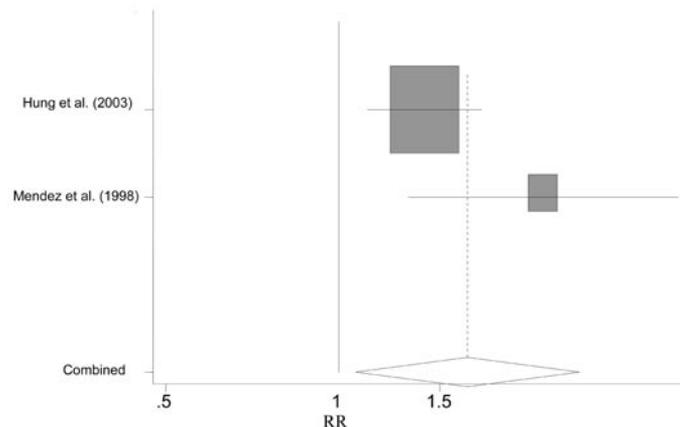
*Arteriosclerosis obliterans*, i.e., peripheral vascular disease (PVD), is the most common cause of arterial obstructive disease of the extremities. The symptoms are intermittent claudication, pain at rest, and trophic changes in the involved limb. The most serious cases require amputation. The pathology is characteristic of typical atheromatous plaques involving the intima of the arteries, often with thrombus formation. The etiology of the disease is the same as with CHD and stroke, but here, smoking is definitely the most important risk factor (Hiatt, 2004).

Mendez *et al.* (1998) examined 1231 men participating in the Dental Longitudinal Study and observed about a two-fold increase in the risk of PVD among those who had periodontal disease at baseline. This relation was significant even after the adjustment for age, BMI, family history of heart disease, and smoking, and exhibited an RR of 2.27 (CI 1.32-3.90,  $p = 0.003$ ). This result is not surprising when we consider the underlying etiopathogenesis of PVD. This condition shares pathogenic pathways that are similar to those of other atherosclerotic diseases.

Recently, Hung and colleagues (2003) also reported a similar but slightly lower increase in the risk of PVD for those patients who had periodontal disease at baseline (RR 1.41, CI 1.12-1.77), after adjustment for age, smoking, BMI, family history of heart disease, hypertension, diabetes, hypercholesterolemia, and occupation. When we re-analyzed the risk of 1.41 by the method of



**Figure 2.** Meta-analysis of periodontal disease and risk of ischemic stroke. Reproduced with permission (Janket *et al.*, 2003).



**Figure 3.** Meta-analysis of periodontitis and peripheral vascular disease. The analysis was performed according to Janket *et al.* (2003).

Rosner *et al.* (1990), the estimate of the relative risk became 1.77. If, in the latter case, one undertakes a meticulous adjustment of confounding factors, these two relative risks appear to be in complete agreement. The weighted average of these two epidemiologic studies is presented in Fig. 3. We can conclude that periodontal disease appears to increase the risk of PVD. However, this statement needs to be confirmed by further studies.

### (IX) Conclusions

Several reviews have been written on the possible association between oral infection and CVD, and although these publications review the same literature, the interpretation and conclusions from the different authors are not consistent. In the present paper, we have reviewed all the published evidence up to March, 2004, regarding the relationship, if any, between oral health parameters and atherosclerosis and cardiovascular diseases. It appears that most experimental and clinical studies reported a small but significant association between oral infections, mostly periodontitis, and CVD. The possible mechanisms by which oral infections might contribute to CVD include the following: a direct effect of micro-organisms in atheroma formation in the endothelium, indirect host-mediated responses, or a genetic predisposition for the pathogenesis.

The crucial causal relation might be established by prospective treatment studies, such as those conducted by Iwamoto *et al.* (2003) and D'Aiuto *et al.* (2004), which elucidate the connection between treatment of poor dental health and systemic inflammatory markers. With respect to the association or relationship of oral diseases and CVD, currently periodontitis appears to increase the risk of stroke and, to a lesser extent, CHD. Although the published data are sparse, periodontal disease also appears to increase the risk of PVD. Whether these associations have any meaningful clinical impact in the initiation and progression of CVD is not clear, even though infection appears to modify, if not trigger, atherosclerosis. If this ultimately turns out to be the case, such a finding could open new prospects for prevention. Meanwhile, we agree with Lowe (2004) who, in his recent comment paper in the American Heart Association journal *Circulation*, states that the answer to the question, "Should dental health scores be used in addition to classical risk factors to predict an individual's risk of CHD and stroke?" simply is, "We do not know." Similarly, the answer to the question, "Does treatment of poor

dental health reduce such risk?" is also, "We do not know."

However, based on the present literature referenced, a cautious "yes" to these questions might be a reality in the future. There are now several short-term intervention studies reporting that treatment of periodontitis reduces the serum concentrations of inflammatory markers, such as CRP, TNF- $\alpha$ , IL-6, which are thought to be initiating factors of CHD. Nevertheless, further studies should investigate more thoroughly the effect of dental treatment on systemic markers of inflammation and hemostasis, the associations of pro-inflammatory genetic polymorphism with oral health parameters, CHD, and stroke. Long-term observations of oral health status, inflammatory and hemostatic markers, and risk of CVD are also definitely needed.

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