

# Periodontal Disease and Coronary Heart Disease Risk

Philippe P. Hujoel, PhD

Mark Drangsholt, DDS, MPH

Charles Spiekerman, PhD

Timothy A. DeRouen, PhD

SEVERAL INFECTIOUS DISEASES have been implicated as possibly causing myocardial infarction (MI).<sup>1</sup> In related research, periodontal disease has also been related to coronary heart disease (CHD). Several observational studies have indicated that periodontitis, a chronic inflammatory periodontal disease that results in the breakdown of bone that surrounds teeth, may be associated with an increased risk for MI.<sup>2-4</sup> At least one cohort study indicated that gingivitis, an inflammatory periodontal disease without the breakdown of supporting bone, also increased the risk for fatal MI.<sup>5</sup> Both the chronic low-level bacteremia that occurs with brushing or chewing and the elevation of inflammatory mediators in response to the bacterial biofilm growing on teeth<sup>6-11</sup> have been suggested as possible causal pathways for the increased risk of MI.

Since periodontal disease and heart disease are common, quantifying their association is of significant public health importance. The interpretation of the reported associations is difficult.<sup>12</sup> On the one hand, the associations could be interpreted as causal, which could imply, as has been suggested, that reducing periodontal disease with interventions may have the additional benefit of reducing the risk of cardiovascular disease (CVD).<sup>13</sup> On the other hand, these

**Context** Research has suggested a relationship between periodontal disease and coronary heart disease (CHD), but data on the association between these 2 common conditions are inconclusive due to the possibility of confounding.

**Objective** To evaluate the risk of CHD in persons with periodontitis, gingivitis, or no periodontal disease.

**Design** Prospective cohort study.

**Setting** The First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, conducted in 1982-1984, 1986, 1987, and 1992.

**Participants** A total of 8032 dentate adults aged 25 to 74 years with no reported history of cardiovascular disease, including 1859 individuals with periodontitis, 2421 with gingivitis, and 3752 with healthy periodontal tissues.

**Main Outcome Measure** First occurrence of death from CHD or hospitalization due to CHD, or revascularization procedures, obtained from death certificates and medical records, by baseline periodontal status.

**Results** During follow-up, 1265 individuals had at least 1 CHD event, including CHD fatality (n=468) or at least 1 hospitalization with a diagnosis of CHD (n=1022), including coronary revascularization procedures (n=155). After adjustment for known cardiovascular risk factors, gingivitis was not associated with CHD (hazard ratio, 1.05; 95% confidence interval, 0.88-1.26), while periodontitis was associated with a nonsignificant increased risk for CHD event (hazard ratio, 1.14; 95% confidence interval, 0.96-1.36).

**Conclusion** This study did not find convincing evidence of a causal association between periodontal disease and CHD risk.

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data could be interpreted as being artifacts, that is, the result of biases caused by confounding.<sup>14</sup> Since periodontitis and myocardial disease share common risk factors, such as increasing age, smoking, stress, socioeconomic status, and body fat content, the potential for confounding is substantial. One recent meta-analysis suggested that incomplete adjustment for socioeconomic status may be responsible for the observed weak associations.<sup>15</sup>

The primary goal of this study was to evaluate 3 periodontal conditions (periodontitis, gingivitis, and periodontal health [no gingivitis or periodontitis]) at baseline and the incidence of the first subsequent CHD event observed within the First National Health and Nutrition

Examination Survey (NHANES I) Epidemiologic Follow-up Study.

## METHODS

### Study Population

The design and sampling of NHANES I (1971-1975) and the epidemiologic follow-up study as it relates to dental

**Author Affiliation:** Department of Dental Public Health Sciences, School of Dentistry (Drs Hujoel, Drangsholt, Spiekerman, and DeRouen), Department of Epidemiology, School of Public Health (Dr Hujoel), Department of Oral Medicine, School of Dentistry (Dr Drangsholt), Department of Biostatistics, School of Public Health (Dr DeRouen), and Department of Medicine, Cardiovascular Health Research Unit (Dr Spiekerman), University of Washington, Seattle.

**Corresponding Author and Reprints:** Philippe P. Hujoel, PhD, Department of Dental Public Health Sciences, School of Dentistry, Box 357475, University of Washington, Seattle, WA 98195 (e-mail: hujoel@u.washington.edu).

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and cardiovascular studies have been reported.<sup>2</sup> Briefly, a US population-based probability sample of civilian noninstitutionalized individuals was obtained. Low-income groups, women of childbearing age, and elderly persons were oversampled. The NHANES I Epidemiologic Follow-up Study is a prospective study of the NHANES I participants who were aged 25 to 74 years at baseline: 8032 dentate individuals who had both a medical and dental examination, reported no history of CVD, and had 4 completed longitudinal follow-ups: 1982 to 1984, 1986 (only those individuals who were 55-74 years at baseline), 1987, and 1992.

### Outcome and Exposure Definition

The baseline information included a medical examination, a standardized medical history and dental examination, laboratory tests, and a single 24-hour dietary recall. Demographic variables in the risk models of each examined person included age at baseline, sex, race (white, African American, and other), education, poverty index (defined in TABLE 1), and marital state (ever married vs never married). Cardiovascular risk factors evaluated at the baseline clinical examination included systolic and diastolic blood pressure, serum cholesterol level, history of diabetes mellitus, physical activity (individuals were defined as physically active if they reported being either very active in their usual day, aside from recreation, or if they reported much exercise for recreation), height and weight, alcohol consumption (glasses per day), smoking duration (years), the average number of cigarettes smoked per day during the smoking years, and a history of a nervous breakdown. For smoking, information regarding the duration of smoking and the average number of cigarettes smoked prior to the baseline examination (1971-1975) was derived from 16 questions asked during the interview in 1982 to 1984. Validation studies have indicated that surrogate response and self-response on cigarette smoking obtained approximately 10 years after the baseline interview (1971-1975) were

not remarkably different from the follow-up interview (1982-1984).<sup>16,17</sup>

A CHD event was defined as 1 of the following outcomes: (1) death with an underlying cause of death coded 410-414 using the *International Classification of Diseases, Ninth Revision (ICD-9)*; (2) a hospital stay with a discharge diagnosis code 410-414 using the *ICD-9CM*; or (3) either of the following coronary revascularization procedures: 36.10-36.19 (coronary revascularization) or 36.00-36.09 (removal of coronary obstruction). The first occurrence of any of these 3 events (fatalities, hospitalization because of CHD, or hospitalization because of revascularization) was used as the defining event.

Three mutually exclusive periodontal classifications were defined based on the Russell Periodontal Index<sup>18</sup>:

periodontitis (n=1859), gingivitis (n=2421), and periodontal health (Periodontal Index <.05; n=3752). Individuals with periodontitis had a periodontal pocket with attachment loss (ie, not merely a deepened gingival crevice due to swelling in the free gingiva). Individuals with gingivitis had an overt area of inflammation, which may have completely circumscribed the tooth and which may have been associated with pseudopockets. The following signs of overt inflammation were separately assessed during the dental examination: bleeding gums, diffuse marginal inflammation, and swollen red papillae. Individuals with either periodontitis or gingivitis were subdivided into groups with and without any of these 3 overt signs of clinical inflammation. Based on the Russell Periodontal Index, 4 levels of

**Table 1.** Baseline Demographics and Cardiovascular Risk Factors According to Dental Status\*

Baseline Characteristics	Periodontitis (n = 1859)	Gingivitis (n = 2421)	Healthy Periodontium (n = 3752)
<b>Demographics</b>			
Age, y	52.4 (0.5)†	43.0 (0.4)	42.0 (0.5)
Male, %	50.4 (1.3)†	38.4 (1.0)†	30.5 (2.2)
Race, %			
White	70.2 (2.7)†	77.5 (2.1)†	88.7 (1.1)
African American	28.0 (2.7)†	21.1 (2.1)†	10.4 (1.1)
Other	1.7 (0.4)	1.4 (0.2)	1.0 (0.2)
Education, y	9.6 (0.2)†	11.1 (0.2)†	12.4 (0.1)
Poverty index‡	226.6 (8.7)†	253.8 (8.4)†	306.7 (6.2)
Never married, %	6.6 (0.7)	7.8 (0.6)	7.4 (0.5)
<b>Cardiovascular risk factors</b>			
Systolic blood pressure, mm Hg	139.9 (0.7)†	129.6 (0.7)	127.5 (0.6)
Diastolic blood pressure, mm Hg	86.5 (0.4)†	82.0 (0.4)	80.1 (0.3)
Total serum cholesterol level mmol/L	5.8 (0.04)†	5.6 (0.03)	5.5 (0.02)
mg/dL	222.1 (1.4)†	215.4 (1.2)	212.74 (0.9)
Diabetes mellitus, %	5.2 (0.5)†	2.7 (0.4)	2.0 (0.2)
Much exercise or very active, %	50.9 (1.7)	53.1 (1.6)	51.9 (0.9)
Body mass index, kg/m <sup>2</sup>	26.2 (0.2)†	25.9 (0.1)†	24.9 (0.1)†
Weight, kg	72.9 (0.5)†	71.8 (0.3)†	69.1 (0.3)
Height, m	1.67 (0.0)	1.66 (0.0)	1.66 (0.0)
Alcohol consumption, glasses per day	0.81 (0.06)†	0.73 (0.04)†	0.55 (0.03)
<b>Smoking</b>			
Pack-years	15.9 (0.7)†	10.4 (0.5)†	8.8 (0.4)
No. of years	15.1 (0.5)†	9.6 (0.3)	8.7 (0.3)
Packs per day	0.59 (0.02)†	0.53 (0.02)†	0.46 (0.01)
Nervous breakdown, %§	3.9 (0.4)†	2.4 (0.4)	2.3 (0.3)

\*Data are given as mean (SE).

†Statistically significant differences ( $P < .005$ ) vs individuals with a healthy periodontium.

‡The poverty index was determined by the poverty income ratio, which is the total household income in the numerator and a multiple of the total income necessary to maintain a family with a given characteristic on a nutritionally adequate food plan in the denominator.

§Physician diagnosis of nervous breakdown as reported by survey participant.

periodontal disease severity were defined, and dose-response relationships were evaluated.

### Statistical Methods

Cox proportional hazard models were fitted to assess whether individuals with periodontitis or gingivitis at baseline were at higher risk for a CHD event than individuals with no signs of periodontal disease at baseline. Time-on-study was used as the time scale for all time-to-event analyses. Potentially confounding variables were included in the model using a forward elimination process.<sup>19</sup> With this approach, potentially confounding variables representing competing hypotheses were added to the model. Since the use of ratios such as body mass index (calculated as weight in kilograms divided by the square of height in meters) and pack-years can induce spurious correlations,<sup>20</sup> factors and interaction terms rather than ratios were modeled. Three different approaches for taking into account the sampling design were evaluated: a model-based analysis assuming the sample was a simple random sample,<sup>21</sup> a design-based analysis taking into account the stratification and clustering but ignoring the sampling weights,<sup>22</sup> and a design-based analysis incorporating the clustering, stratification, and the sampling weights.<sup>23</sup> Which analysis is appropriate is a subtle question<sup>22</sup> that depends on a trade-off between efficiency and bias. The primary results reported in the tables take into account

the sampling design but not the sampling weights. This approach was selected because the sampling weights are primarily determined by design variables, such as age, race, poverty census enumeration district, and family income.<sup>21</sup> Since these design variables were partially captured by the socioeconomic variables included in the statistical models, not using the sampling weights in the analyses provides a good compromise between bias and efficiency.<sup>22</sup> Since the associations between periodontitis and CHD were small and sensitive to the analytic approach selected, all 3 approaches were presented for the key results so that the robustness of the conclusions could be evaluated. Analyses that adjusted for the sampling design and/or weights were performed using SUDAAN software.<sup>24,25</sup> Individuals with evidence of prior CVD (a report of a prior MI, stroke, heart failure, or use of medication for a weak heart) were excluded from the primary analyses. Baseline differences were assessed using analysis of variance models for continuous variables and logistic regression models for binary variables. Post hoc power estimates were computed based on the normal distributions of the regression coefficient estimates as  $1 - \beta = \Phi(1.96 + |\log(\text{hazard ratio [HR]})|/\text{SE})$ .

## RESULTS

### Baseline Findings

Periodontal status was significantly associated with demographic factors, life-

style characteristics, and medical conditions (Table 1). When compared with individuals with a healthy periodontium, individuals with periodontitis and gingivitis were significantly more likely to be male, less educated, African American, and poorer ( $P < .005$ ). Individuals with periodontitis were also older and significantly different from individuals with a healthy periodontium ( $P < .005$ ) with respect to most cardiovascular risk factors. These individuals also were more likely to have diabetes mellitus, be overweight, consume more alcohol and cigarettes, have higher systolic and diastolic blood pressure, have higher serum cholesterol levels, and have had a nervous breakdown ( $P < .005$  for all comparisons). Individuals with gingivitis were similar to individuals with a healthy periodontium with respect to many cardiovascular risk factors with the exception of body mass index, weight, alcohol consumption, and pack-years of smoking ( $P < .005$  for all comparisons).

### Periodontitis and CVD Risk

During the follow-up, 1265 individuals had at least 1 CHD event: CHD fatality ( $n = 468$ ), hospitalization for CHD ( $n = 1022$ ), or hospitalization for coronary revascularization procedure ( $n = 155$ ). Unadjusted for any potentially confounding variables and excluding individuals with evidence of prior CVD, individuals with periodontitis had an HR of 2.66 (95% confidence interval [CI], 2.34-3.03) for a CHD event when

**Table 2.** Hazard Ratios (HRs) for CHD Events and CHD Mortality Associated With Periodontitis and Gingivitis\*

CHD Events, HR (95% CI)		CHD Fatalities, HR (95% CI)		Variables Adjusted for in the Model			
Periodontitis†	Gingivitis‡	Periodontitis†	Gingivitis‡	DMG/SES§	CVR1	CVR2	Sample Design¶
2.66 (2.34-3.03)	1.20 (1.05-1.39)	3.09 (2.50-3.81)	1.20 (0.94-1.52)				
1.24 (1.08-1.43)	1.02 (0.88-1.18)	1.28 (1.02-1.61)	0.99 (0.77-1.28)	✓			
1.14 (0.98-1.33)	1.03 (0.88-1.21)	1.19 (0.91-1.55)	1.09 (0.82-1.45)	✓	✓		
1.14 (0.96-1.35)	1.05 (0.88-1.25)	1.21 (0.90-1.62)	1.17 (0.86-1.59)	✓	✓	✓	
1.14 (0.96-1.36)	1.05 (0.88-1.26)	1.20 (0.90-1.61)	1.17 (0.84-1.61)	✓	✓	✓	✓

\*Coronary heart disease (CHD) events include revascularization, nonfatal myocardial infarction, and fatal CHD. CI indicates confidence interval. Comparisons vs individuals with healthy periodontium.

†Individuals with periodontitis had a periodontal pocket with attachment loss (ie, not merely a deepened gingival crevice due to swelling in the free gingiva).

‡Individuals with gingivitis had an overt area of inflammation, which may have completely circumscribed the tooth and which may have been associated with pseudopockets.

§DMG/SES indicates demographics and socioeconomic status. Includes age, age squared, sex, race (2 indicator variables for African American and other), poverty index (defined in Table 1), marital status, education, and an interaction term for marital status and sex.

||CVR indicates cardiovascular risk factors. CVR1: Log (smoking duration), No. of cigarettes per day, diastolic blood pressure, systolic blood pressure, serum cholesterol levels, and diabetes mellitus. CVR2: Log (height), log (weight), log (No. of glasses of alcohol per day), physical activity (indicator variable for heavy recreational or nonrecreational physical activity), and nervous breakdown.

¶Sample design: Multistage cluster sampling without replacement.

compared with those individuals with a healthy periodontium (TABLE 2). After adjustment for confounders and sampling design, the HR of CHD for individuals with periodontitis decreased to 1.14 (95% CI, 0.96-1.36). Adjustment for the sampling weights increased the HR by 6% to a value of 1.21 (95% CI, 0.98-1.50).

Various dose-response relationships and subgroup analyses were explored (TABLE 3). When the analyses were restricted to individuals with periodontitis, no dose-response relationships were found between the number of teeth at baseline and CHD risk. Among individuals with periodontitis, the presence of either swollen papillae, diffuse marginal inflammation, or bleeding gums did not elevate the risk for CHD (HR, 0.98; 95% CI, 0.74-1.29). No obvious dose-response relationships were detected between the severity of the periodontitis and CHD risk (Table 3). Individuals within the upper level of periodontal disease severity were not at elevated risk for CHD (HR, 1.28; 95% CI, 0.87-1.88).

When the analyses were limited to nonsmoking individuals at baseline, the HR was attenuated (HR, 1.06; 95% CI, 0.84-1.34). When the analyses were limited to individuals younger than 50 years, the HR associated with periodontitis was 1.36 (95% CI, 0.97-1.92). When the analyses were stratified by 10-year age groups, no simple age-related patterns became apparent. Stratifying by measures of socioeconomic class did not lead to any substantial changes in the HR estimates. Individuals within the lowest quartile of the poverty index had an HR of 1.09 (95% CI, 0.80-1.48) associated with periodontitis, while individuals within the upper quartile of the poverty index had an HR of 1.12 (95% CI, 0.82-1.53) associated with periodontitis.

When only fatalities were evaluated, periodontitis was associated with an HR for cardiovascular mortality of 1.20 (95% CI, 0.90-1.61) (Table 2). For cardiovascular mortality, the sampling weights increased the HR by 21.7% to 1.46 (95% CI, 0.94-2.27).

### Gingivitis and CHD Risk

Unadjusted for confounding variables, gingivitis was associated with a 20% increased risk for CHD events when compared with a healthy periodontium (HR, 1.20; 95% CI, 1.05-1.39) (Table 2). After adjustment for potentially confounding variables and the sampling design, gingivitis was not associated with an increased risk of CHD (HR, 1.05; 95% CI, 0.88-1.26). Inclusion of the sampling weights led to a slightly protective association (HR, 0.88; 95% CI, 0.69-1.11). The presence of overt signs of clinical inflammation in combination with gingivitis did not increase CHD risk (HR, 0.99; 95% CI, 0.75-1.31) (Table 3). There was no association between gingivitis and fatal CHD disease (HR, 1.17; 95% CI, 0.84-1.61) (Table 2).

### Overt Signs of Clinical Inflammation and CHD Risk

Separate analyses were performed to evaluate whether signs of periodontal inflammation, regardless of the diagnosis of gingivitis or periodontitis, were associated with CHD risk. After adjustment for confounding variables and sampling design, there was no association between CHD and the presence of red swollen papillae (HR, 1.06; 95% CI, 0.87-1.28) and between CHD and the presence of diffuse marginal inflammation (HR, 1.05; 95% CI, 0.88-1.25). Bleeding gums were associated with a nonsignificantly increased CHD risk (HR, 1.24; 95% CI, 0.77-2.00).

### Power

Post hoc power calculations indicated that the statistical model used to relate CHD events (fatal MI, nonfatal MI, and revascularization procedures) had greater than 90% power to detect a 30% increased CHD risk associated with periodontitis or gingivitis (type I error rate, 5%).

### COMMENT

The results of this study do not provide convincing evidence that periodontitis and gingivitis are associated with CHD. Gingivitis was not associated with CHD. Periodontitis was associated with a nonsignificant increased risk for CHD. Mark-

**Table 3.** Dose-Response Relationships and Subgroup Analyses Between Coronary Heart Disease Events and Periodontal Disease\*

Periodontitis	Hazard Ratio (95% CI)
No. of teeth at baseline	
25-32	Reference group
17-24	0.84 (0.64-1.09)
11-16	0.75 (0.51-1.10)
4-10	0.88 (0.62-1.25)
Severity (Russell Index <sup>18</sup> )	
No periodontitis or gingivitis	Reference group
≤2.9	1.18 (0.90-1.53)
2.9≤4.4	1.26 (0.96-1.65)
4.4≤6.0	1.13 (0.90-1.43)
6.0-8.0	1.28 (0.87-1.88)
Age groups (stratified), y	
25-34	1.11 (0.58-2.12)
35-44	1.80 (1.04-3.10)
45-54	1.53 (0.94-2.47)
55-64	1.01 (0.75-1.37)
65-74	0.94 (0.68-1.29)
Clinical inflammation†	
Gingivitis	
Without	Reference group
With	0.99 (0.75-1.31)
Periodontitis	
Without	Reference group
With	0.98 (0.74-1.29)

\*Coronary heart disease events include revascularization, nonfatal myocardial infarction, and fatal coronary heart disease. CI indicates confidence interval. Adjusted for the sampling design and the potentially confounding variables that are listed in Table 1.

†Clinical inflammation was defined as the presence of bleeding gums, swollen red papillae, or diffuse marginal inflammation.

ers of periodontal inflammation associated with either periodontitis or gingivitis, such as swollen red papillae, bleeding gums, or diffuse marginal inflammation, were not associated with an increased risk for CHD. No obvious dose-response relationships were present between the severity of periodontitis and CHD risk. The findings of this study do not provide the kind of consistent evidence needed to support the hypothesis of a causal relationship between periodontal disease and CHD.

Gingivitis was not associated with CHD. Subgroup analyses by gingivitis severity further corroborated this conclusion with more severe gingivitis not being associated with any increased risk for CHD. This finding is important since an estimated 50% of the US adult population has gingivitis.<sup>26</sup> Even a small elevated risk for CHD associated with gingivitis would result in a substantial attributable proportion. This finding is in contrast to the findings based on the Nutrition Canada Survey in which gin-



ginitis was associated with an increased fatal MI risk.<sup>5</sup>

Slightly positive associations between periodontitis and CHD events were identified. The relevance, if any, of these associations is uncertain. No clear statistical significance or dose-response trends were observed. Our study is currently one of the largest investigations on the association between periodontal disease and CHD. With 1265 events, long follow-up, extensive information on potentially confounding variables, and sufficient statistical power (>90%) to detect small associations (HR, 1.3), this study had a good chance to reliably identify small associations. Not observing clearly significant associations despite the extensive data manipulations in the search of significance suggests that the true association between periodontitis and CHD is either absent or so small that even larger studies are required to identify them.

Various subgroup analyses and dose-response relationships between periodontitis and CHD were explored. Coronary heart disease risk did not increase substantially with the severity of periodontitis. No relationship was identified between the number of teeth in patients with periodontitis and CHD risk. There was no association between markers of clinical inflammation and CHD, which is inconsistent with the current hypothesized causal role of periodontal inflammation<sup>6</sup> in CHD.

When sampling weights were included in the analyses, periodontitis tended to increase CHD risk. Conversely, inclusion of sampling weights led to small protective effects associated with gingivitis. These small risk increases and decreases, depending on the particular analytic approach used, further strengthened the impression of no association.

A review of recent studies does not provide convincing support in favor of a causal association.<sup>15</sup> Two large cohort studies in socially homogeneous populations with similar health awareness and rigorous control for confounders reported no associations between periodontitis and CHD.<sup>27,28</sup> Less well-controlled studies, studies in socially het-

erogeneous populations, such as this one, without control for health awareness, or studies with few events reported small-to-moderate associations.<sup>2,4,29,30</sup> In particular, insufficient control for smoking history, socioeconomic status, and health awareness may have induced small positive associations.

While this study did provide convincing evidence regarding the absence of a moderate-to-large association between periodontitis and CHD, a small causal association could not be ruled out. Several biological mechanisms through which periodontal disease may cause CHD have been proposed as follows: the invasion into endothelial coronary cells by oral microorganisms,<sup>32,33</sup> the harmful cardiovascular effects of inflammatory response to periodontitis,<sup>6</sup> or contributions of oral microorganisms to acute thromboembolic events during bacteremia.<sup>34</sup> If these biological mechanisms are responsible for a slight risk increase, better controlled and still larger studies will be required to identify them. Such efforts may be important because of the high prevalence of periodontitis.

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## REFERENCES

1. Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease. *Lancet*. 1997;350:430-436.
2. DeStefano F, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. *BMJ*. 1993;306:688-691.
3. Mattila KJ. Dental infections as a risk factor for acute myocardial infarction. *Eur Heart J*. 1993;14:51-53.
4. Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. *J Periodontol*. 1996;67:1123-1137.
5. Morrison HI, Ellison LF, Taylor GW. Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. *J Cardiovasc Risk*. 1999;6:7-11.
6. Beck JD, Offenbacher S, Williams R, Gibbs P, Garcia R. Periodontitis: a risk factor for coronary heart disease? *Ann Periodontol*. 1998;3:127-141.
7. Meyer DH, Fives-Taylor PM. Oral pathogens: from

dental plaque to cardiac disease. *Curr Opin Microbiol*. 1998;1:88-95.

8. Slavkin HC. Does the mouth put the heart at risk? *J Am Dent Assoc*. 1999;130:109-113.
9. Valtanen VV. Infection as a risk factor for infarction and atherosclerosis. *Ann Med*. 1991;23:539-543.
10. Mattila KJ, Valtanen VV, Nieminen MS, Asikainen S. Role of infection as a risk factor for atherosclerosis, myocardial infarction, and stroke. *Clin Infect Dis*. 1998;26:719-734.
11. Kweider M, Lowe GD, Murray GD, et al. Dental disease, fibrinogen and white cell count; links with myocardial infarction? *Scott Med J*. 1993;38:73-74.
12. Slots J. Casual or causal relationship between periodontal infection and non-oral disease? *J Dent Res*. 1998;77:1764-1765.
13. Newman HN. Periodontal therapeutics—a viable option? *Int Dent J*. 1998;48:173-179.
14. Joshipura KJ, Douglass CW, Willett WC. Possible explanations for the tooth loss and cardiovascular disease relationship. *Ann Periodontol*. 1998;3:175-183.
15. Danesh J. Coronary heart disease, *Helicobacter pylori*, dental disease, *Chlamydia pneumoniae*, and cytomegalovirus. *Am Heart J*. 1999;138:S434-S437.
16. McLaughlin JK, Dietz MS, Mehl ES, Blot WJ. Reliability of surrogate information on cigarette smoking by type of information. *Am J Epidemiol*. 1987;126:144-146.
17. Machlin SR, Kleinman JC, Madans JH. Validity of mortality analysis based on retrospective smoking information. *Stat Med*. 1989;8:997-1009.
18. Russell AL. A system of scoring for prevalence surveys of periodontal disease. *J Dent Res*. 1956;35:350-359.
19. Maclure M. Multivariate refutation of aetiological hypotheses in non-experimental epidemiology. *Int J Epidemiol*. 1990;19:782-787.
20. Kronmal RA. Spurious correlation and the fallacy of the ratio standard revisited. *J R Stat Soc A STA*. 1993;156:379-392.
21. Breslow RA, Wideroff L, Graubard BI, et al. Alcohol and prostate cancer in the NHANES I Epidemiologic Follow-up Study. *Ann Epidemiol*. 1999;9:254-261.
22. Korn EL, Graubard BI. Epidemiologic studies utilizing surveys. *Am J Public Health*. 1991;81:1166-1173.
23. Kish L, Frankel MR. Inference from complex samples. *J R Stat Soc Serv B*. 1974;36:1-37.
24. Graubard BI, Korn EL. Analyzing health surveys for cancer-related objectives. *J Natl Cancer Inst*. 1999;91:1005-1016.
25. Shah BV, Barnwell BG, Bieler GS. *SUDAAN User's Manual, Release 7.5*. Research Triangle Park, NC: Research Triangle Institute; 1997.
26. Albandar JM, Kingman A. Gingival recession, gingival bleeding, and dental calculus in adults 30 years of age and older in the United States, 1988-1994. *J Periodontol*. 1999;70:30-43.
27. Christen WG, Hennekens CH, Ajani UA, Ridker PM. Periodontal disease and risks of cardiovascular disease. *Circulation*. 1998;97:821.
28. Joshipura KJ, Rimm EB, Douglass CW, et al. Poor oral health and coronary heart disease. *J Dent Res*. 1996;75:1631-1636.
29. Mattila KJ, Nieminen MS, Valtanen VV, et al. Association between dental health and acute myocardial infarction. *BMJ*. 1989;298:779-781.
30. Wu T, Trevisan M, Genco R, Dorn J, Falkner K, Sempos C. Periodontal disease as a risk factor for CVD, CHD, and stroke. *Circulation*. 1999;99:8.
31. Deshpande RG, Khan MB, Genco CA. Invasion of aortic and heart endothelial cells by *Porphyromonas gingivalis*. *Infect Immun*. 1998;66:5337-5343.
32. Dorn BR, Dunn WA Jr, Progulsk-Fox A. Invasion of human coronary artery cells by periodontal pathogens. *Infect Immun*. 1999;67:5792-5798.
33. Herzberg MC, Weyer MW. Dental plaque, platelets, and cardiovascular diseases. *Ann Periodontol*. 1998;3:151-160.
34. Herzberg MC, Meyer MW. Effects of oral flora on platelets. *J Periodontol*. 1996;67:1138-1142.