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Age-Dependent Associations Between Chronic Periodontitis/Edentulism and Risk of Coronary Heart Disease

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Background—Several epidemiological studies have suggested periodontitis as a risk factor for coronary heart disease (CHD), but results have been inconsistent.

Methods and Results—We evaluated the association between clinical and radiographic measures of periodontitis, edentulism, and incident CHD (angina, myocardial infarction, or fatal CHD) among 1203 men in the VA Normative Aging and Dental Longitudinal Studies who were followed up with triennial comprehensive medical and dental examinations up to 35 years (median 24 years). Cox proportional hazards models with time-varying effects of exposure and potential confounders were fit. We found a significant dose-dependent association between periodontitis and CHD incidence among men <60 years of age (hazard ratio 2.12, 95% confidence interval 1.26 to 3.60 comparing highest versus lowest category of radiographic bone loss, P for trend=0.02), independent of age, body mass index, smoking, alcohol intake, diabetes mellitus, fasting glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, hypertension, systolic and diastolic blood pressure, education, marital status, income, and occupation. No association was found among men >60 years of age. Similar results were found when the sum of probing pocket depths was used as a measure of periodontitis. Among men ≥60 years of age, edentulous men tended to have a higher risk of CHD than dentate men in the lowest bone loss (hazard ratio 1.61, 95% confidence interval 0.95 to 2.73) and lowest pocket depth (hazard ratio 1.72, 95% confidence interval 1.03 to 2.85) categories, independent of confounders.

Conclusions—Chronic periodontitis is associated with incidence of CHD among younger men, independent of established cardiovascular risk factors. (***Circulation*. 2008;117:1668-1674.**)

Key Words: coronary disease ■ epidemiology ■ infection ■ inflammation ■ risk factors

Several cohort studies have found an association between chronic periodontitis and the risk of coronary heart disease (CHD), independent of a variety of potential confounders.[1,2] However, other studies did not find significant associations after adjustments for important confounding factors.[3,4] These inconsistencies have led to concerns and uncertainties about the validity of the periodontitis–CHD association and its strength. Such concerns include residual confounding by smoking[5] and potential misclassification of periodontitis in studies not employing periodontal probing for assessment of periodontitis.[1,3,4,6,7] Indeed, the attenuation of relative risk estimates due to such misclassification can be quite dramatic[8] and may explain, at least in part, some of the null results found in several large cohorts.

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A different but related issue pertains to the operationalization and definition of chronic periodontitis as the exposure of interest. Periodontitis is clinically assessed by measuring periodontal probing depth and attachment level at various sites of the dentition or by measuring alveolar bone loss from radiographs. Definitions of periodontitis in clinical research are based on either measure or on combinations thereof and vary widely.[9] The appropriate choice of clinical exposure measure for studies of the association between periodontitis and CHD is a matter for debate.[10] In addition, some authors have argued that the serological response to periodontal pathogens may be a better exposure measure because it also captures the host inflammatory response.[11] Both causal and

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noncausal pathways have been proposed that could explain an association between periodontitis and CHD.[2,12] Although emerging evidence from intervention studies suggests that successful treatment of periodontitis may have beneficial effects on surrogate cardiovascular end points such as inflammatory serum markers[13] and endothelial function,[14] the relevance of these findings on a population level remains uncertain given the inconsistent epidemiological evidence for a periodontitis–CHD association. The purpose of the present study was to evaluate chronic periodontitis and edentulism (complete absence of natural teeth) as risk factors for incident CHD among men using data from the VA Normative Aging and Dental Longitudinal Studies.

Methods

Study Population

Study subjects were participants in the US Department of Veteran Affairs (VA) Normative Aging Study (NAS) who were also enrolled in the Dental Longitudinal Study (DLS). The NAS is an ongoing closed-panel longitudinal study that initially enrolled 2280 healthy male volunteers from the greater Boston, Mass, area beginning in 1961. Men were not VA patients and have continued to receive their medical and dental care in the private sector. Subjects were examined approximately every 3 years by trained VA staff physicians, and such examinations included a medical history, a physical examination, and a variety of biochemical laboratory tests. Diseases and conditions were entered into the database according to the 8th revision of the *International Classification of Diseases* (ICD-8).

Beginning in 1966, a subset of 1231 volunteers 21 to 84 years of age was enrolled in the DLS.[15] The first DLS examination was used as the baseline for the present analyses. We excluded 12 men who had developed CHD before their first DLS examination.

The protocol was approved by the Department of Veterans Affairs Committee on Human Studies, and procedures followed were in accordance with institutional guidelines. All subjects conferred their informed consent before their entry into the study.

Outcome Assessment

Myocardial infarction, angina pectoris, and fatal CHD were considered CHD events and were ascertained in the NAS with the same criteria used in the Framingham Heart Study.[16] Myocardial infarction was diagnosed on the basis of ECG findings, elevation of serum enzymes, and chest discomfort consistent with myocardial infarction or on the basis of autopsy results. Angina pectoris was defined as recurrent chest discomfort related to exertion or excitement that lasted up to 15 minutes that was responsive to rest or nitroglycerin. Fatal CHD was defined as a primary cause of death attributed to CHD based on ICD-8 codes (410–414). Person-time accrued until 2004 was included in these analyses.

Exposure Assessment

A trained and calibrated periodontist conducted comprehensive oral examinations triennially, including full-mouth radiographs and periodontal probing at each tooth. At each examination, periodontitis was assessed both radiographically and clinically. First, alveolar bone loss was assessed on each tooth on all interproximal surfaces. A bone loss score was assigned to each mesial and distal tooth site in 20% increments (score 0: no bone loss; score 1: bone loss $\leq$20%; score 2: bone loss $>$20% and $\leq$40%; score 3: bone loss $>$40% and $\leq$60%, score 4: bone loss $>$60% and $\leq$80%, score 5: bone loss $>$80%). Second, the maximum probing pocket depth was recorded for each tooth by calibrated examiners and recorded as a score (0 to 3 mm, $>$3 to 5 mm, or $>$5 mm). More detailed descriptions of the periodontal measures used in the DLS and their reproducibility have been published previously.[17,18] Briefly, weighted κ-values for interexaminer reproducibility of probing depth and bone loss scores indicated good reproducibility ($\kappa>0.4$)[19] based on repeat assessments on 24 and 25 subjects, respectively.

Other Variables

Blood pressure was measured by standard mercury sphygmomanometer in each arm in seated subjects. Mean readings from both arms were used for systolic and diastolic blood pressure. Body mass index was calculated from measured weight and height.

Laboratory parameters determined from fasting serum samples included concentrations of total cholesterol, HDL cholesterol (beginning in 1981), triglycerides, and glucose. In addition, a 2-hour oral glucose tolerance test was performed. Men were classified as diabetic if they had a physician diagnosis of diabetes mellitus or a fasting glucose $\geq$126 mg/dL, or if their 2-hour glucose tolerance test was $\geq$200 mg/dL.

Information on history of cigarette smoking was obtained by interview. Information on smoking intensity, duration, and time since cessation was used to calculate a comprehensive smoking index as described previously.[20]

Daily alcohol consumption was derived from replies to the Cornell Medical Index Health Questionnaire, in which subjects responded as to whether they usually drank 2 or more alcoholic drinks per day (yes/no). Maximum level of education completed was categorized into less than high school education, completed high school, or beyond high school education. Occupation was recorded in 9 categories and referred to former occupation for those men who were retired. Income was assessed at the DLS baseline examination only. Marital status was categorized as a binary variable, married or remarried versus divorced, widowed, single, or separated. With the exception of income, all dental and nondental variables were updated at each triennial examination.

Data Analysis

Summary statistics of baseline characteristics were calculated for the entire cohort and separately for men who had incident CHD or fatal CHD. Person-time for each participant was calculated from their first DLS visit to first CHD event, death, or last NAS visit, whichever occurred first. Two separate outcome definitions were used, total CHD (nonfatal or fatal) and fatal CHD. Each participant contributed only 1 end point for each analysis. Therefore, for the total CHD analyses, once a participant was diagnosed with CHD, they were excluded from analyses. For the fatal CHD analyses, only fatal CHD events were considered cases; therefore, nonfatal cases continued to contribute person-time until death or censoring.

Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals (CIs) for the association between periodontitis or edentulism and incidence of CHD. Two separate exposure definitions of periodontitis were used. First, mean whole-mouth radiographic bone loss score was calculated as a cumulative measure of periodontitis history. Second, "cumulative probing depth" was calculated as the whole-mouth sum of pathologically increased probing depth ($>$3 mm) using the midpoints of each recorded category (4 and 6 mm). Tests of linear trend were performed for each model by entering mean bone loss score or cumulative pocket depths as continuous variables. In addition, the exposure measures were categorized. The reference categories were prespecified and included men with no or minimal bone loss (mean bone loss score of 0.5 or less) and no pathological pocketing (no periodontal pockets $>$3 mm, ie, cumulative probing depth $<$4 mm), respectively. Data on periodontitis and edentulism were updated at each DLS examination and modeled as time-varying effects (ie, subjects who became edentulous during follow-up contributed person-time to both exposure categories [periodontitis and edentulism]). Multivariate models adjusted for age, education, income, and occupation at baseline and time-varying effects of smoking, body mass index, high-density lipoprotein cholesterol, total cholesterol, triglycerides, hypertension, mean systolic blood pressure, mean diastolic blood pressure, diagnosis of diabetes mellitus, fasting glucose level, 2-hour glucose level, alcohol consumption, and marital status.

Because of prior evidence for effect modification by age,[1,21–23] all models included interaction terms with age. First, models were stratified by means of a dichotomous cutoff (<60, ≥60 years). For these models, men could change categories during the study (ie, they contributed person-time to both age strata if they became older than the cutoff age during the study). In addition, we used quadratic spline regression[24] to evaluate the effect of time-varying age on the periodontitis/CHD association on a continuous scale, defining knots at the age tertile cutoffs of 57 and 67 years. Likelihood ratio tests were used to test for interactions with age using interaction terms.

All models were evaluated to determine departure from the proportional hazards assumptions with scaled Schoenfeld residual plots for the final multivariate models. We further conducted a sensitivity analysis restricted to never-smokers. We also evaluated the potential for survivorship bias, because all men had to be systemically healthy at baseline to be enrolled in the study. For that purpose, we conducted a sensitivity analysis for men ≥60 years old that compared results between those men who were ≥60 years old at baseline and men <60 years old at baseline. All analyses were performed with STATA 9.0 (Stata Corp, College Station, Tex).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

A total of 1203 men free of CHD enrolled in the DLS. Over a follow-up time of up to 35 years (median 24 years), a total of 364 men were diagnosed with CHD (either fatal or nonfatal), and 109 men died of CHD. Only 6 men were lost to follow-up (ie, no information on either nonfatal CHD incidence or CHD mortality could be collected), and these men contributed no person-time; however, we compared baseline characteristics between 383 men who did not attend an NAS/DLS examination for at least 10 years before death or before the most recent examination cycle and 820 men who did. Men who did not attend an NAS/DLS examination for at least 10 years were significantly older and more likely to be smokers. However, independent of age, no significant differences were found with respect to baseline periodontitis and prevalence of edentulism.

Baseline characteristics for the entire cohort and for men who later developed CHD and fatal CHD are shown in Table 1. At baseline, men who were later diagnosed with CHD, particularly those who died of CHD, tended to be older and had higher serum concentrations of total cholesterol and triglycerides and lower serum concentrations of high-density lipoprotein cholesterol (measured at examination cycle 5), higher systolic blood pressure, higher prevalence of hypertension and diabetes mellitus, and fewer remaining teeth. A modest correlation was present between mean bone loss score and cumulative pocket depth (Spearman $\rho=0.27$).

The association between chronic periodontitis and total CHD was modified by age ($P=0.006$ and $P=0.003$ for interaction between age and mean bone loss score and cumulative probing depth, respectively). Among men <60 years of age, a positive association existed between chronic periodontitis and CHD incidence (Table 2). Men with a mean bone loss score >1.5 (ie, approximate average bone loss >20%) were 112% (95% CI 26% to 260%) more likely to develop CHD than men with a mean bone loss score ≤0.5 (ie, average bone loss ≤5%), independent of other CHD risk factors. For each 20% increase in mean bone loss, the rate of CHD increased by 39% (95% CI 5% to 83%, $P=0.02$).

Table 1. Baseline Characteristics of Men With or Without Incident Total or Fatal CHD During Follow-Up

	No Incident CHD (n=839)	Total CHD (n=364)	Fatal CHD (n=109)
Age, y	48±9	50±9	55±10
Body mass index, kg/m^2	26.0±3.0	26.5±3.2	26.4±3.4
Total cholesterol, mmol/L	221±44	233±52	235±49
HDL, mmol/L*	49±14	46±14	42±12
Triglycerides, mmol/L	148±66	169±114	178±130
Hypertension, %	10	14	17
Systolic blood pressure, mm Hg	123±15	127±16	131±19
Diastolic blood pressure, mm Hg	76±9	78±9	78±10
Diabetes mellitus, %†	6	7	10
Current smokers, %	25	22	24
Alcohol use ≥2 drinks/d, %	23	20	19
Education less than high school, %	11	12	25
Occupation (professional), %	17	19	15
Income, %‡			
<$14 999	30	32	31
$15 000–$24 999	51	49	51
>$25 000	19	19	18
No. of teeth, %			
>20	78	74	63
15–20	9	7	5
10–15	3	5	6
<10	5	6	10
Edentulous	5	8	17

Figures are percentages or mean±SD. HDL indicates high-density lipoprotein.
*HDL cholesterol available beginning in 1981.
†Diabetes based on diagnosis by physician or elevated fasting or 2 hours glucose test.
‡Income at DLS baseline.

Similarly, a statistically significant linear trend was present for increased rates of CHD with increasing cumulative pocket depth (hazard ratio 1.10, 95% CI 1.05% to 1.17% per 10-mm increase in cumulative pocket depth, $P<0.001$). Men with a cumulative pocket depth >40 mm had 94% higher rates (95% CI 23% to 205%) of CHD than younger men with no pathological pockets. Spline regression that evaluated effect modification by age on a continuous scale suggested that the association between periodontitis and CHD was strongest among the youngest men and decreased fairly linearly with age, with no association present among men older than approximately 60 to 65 years of age (Figure 1). This is consistent with the results from the stratified analyses, in which no association was found among older men (Table 2).

A nonsignificant association between edentulism and CHD incidence was present among younger men, although only 9 edentulous men experienced CHD events in this age group. Edentulous men ≥60 years old had 61% (95% CI −5% to 173%) and 72% (3% to 185%) higher rates of CHD than men with a mean bone loss score ≤0.5 and men with no pathological pockets, respectively (Table 2).

Because of the small number of fatal CHD events in men younger than 60 years, estimates were very imprecise and are

Table 2. Association Between Periodontitis and Total Incident CHD by Age (<60, ≥60 Years)

	Age <60 y						Age ≥60 y					
	Median	Teeth Remaining, Median, n	CHD Events, n	Person-Years	HR (95% CI)*	HR (95% CI)†	Median	Teeth Remaining, Median, n	CHD Events, n	Person-Years	HR (95% CI)‡	HR (95% CI)§
MBLS												
<0.5	0.24	27	47	7745	1.00 (Reference)	1.00 (Reference)	0.31	26	42	2338	1.00 (Reference)	1.00 (Reference)
0.5–1	0.71	25	51	4127	1.86 (1.25–2.77)	1.68 (1.13–2.52)	0.76	24	56	3282	0.90 (0.60–1.35)	0.84 (0.56–1.26)
1–1.5	1.21	22	25	2099	1.77 (1.09–2.89)	1.55 (0.94–2.56)	1.22	21	53	2426	1.13 (0.75–1.69)	0.98 (0.61–1.56)
>1.5	1.81	19	22	1329	2.48 (1.49–4.12)	2.12 (1.26–3.60)	1.88	15	34	1491	1.13 (0.71–1.78)	1.81
Edentulous		0	9	683	2.06 (1.01–4.20)	1.90 (0.92–3.93)		0	25	793	1.95 (1.18–3.22)	1.61 (0.95–2.73)
CPD												
0 to <4 mm	0	24	41	5752	1.00 (Reference)	1.00 (Reference)	0	23	48	2823	1.00 (Reference)	1.00 (Reference)
4–20 mm	12	25	36	3952	1.32 (0.84–2.06)	1.26 (0.80–1.98)	12	22	63	3009	1.17 (0.80–1.71)	1.11 (0.77–1.62)
20–40 mm	30	26	29	2797	1.44 (0.89–2.32)	1.42 (0.88–2.29)	30	23	47	1956	1.30 (0.87–1.95)	1.23 (0.82–1.85)
>40 mm	60	26	37	2372	2.09 (1.34–3.26)	1.94 (1.23–3.05)	60	24	26	1680	0.83 (0.51–1.34)	0.73 (0.45–1.19)
Edentulous		0	9	683	1.83 (0.89–3.77)	1.71 (0.82–3.55)		0	25	793	2.04 (1.26–3.33)	1.72 (1.03–2.85)

MBLS indicates mean bone loss score; CPD, cumulative probing depth.

*Adjusted for age. Trend: MBLS, $P=0.001$; CPD, $P<0.001$.

†Adjusted for age, body mass index, high-density lipoprotein cholesterol, total cholesterol, triglycerides, hypertension, mean systolic and diastolic blood pressure, diabetes mellitus, fasting glucose, smoking, alcohol intake, occupation and education, income, and marital status. Trend: MBLS, $P=0.02$; CPD, $P<0.001$.

‡Adjusted for age. Trend: MBLS, $P=0.56$; CPD, $P=0.57$.

§Adjusted for age, body mass index, high-density lipoprotein cholesterol, total cholesterol, triglycerides, hypertension, mean systolic and diastolic blood pressure, diabetes mellitus, fasting glucose, smoking, alcohol intake, occupation and education, income, and marital status. Trend: MBLS, $P=0.99$; CPD, $P<0.33$.

not reported here. Among older men, no significant association was found between either measure of periodontitis and fatal CHD (Table 3); however, edentulous men had significantly increased risk of fatal CHD compared with men with a mean bone loss score ≤0.5 (hazard ratio 4.21, 95% CI 1.57 to 11.3) and men without pathologically increased pocket depth (hazard ratio 2.97, 95% CI 1.41 to 6.25). Finally, results were consistent among never-smokers and between men ≥60 years of age who were younger or older than 60 years when recruited into the study.

Discussion

In this long-term longitudinal cohort study, we found a positive dose-dependent association between chronic periodontitis and incidence of CHD among men <60 years of age, independent of established cardiovascular risk factors. Among older men, no association between periodontitis and incidence of CHD was found.

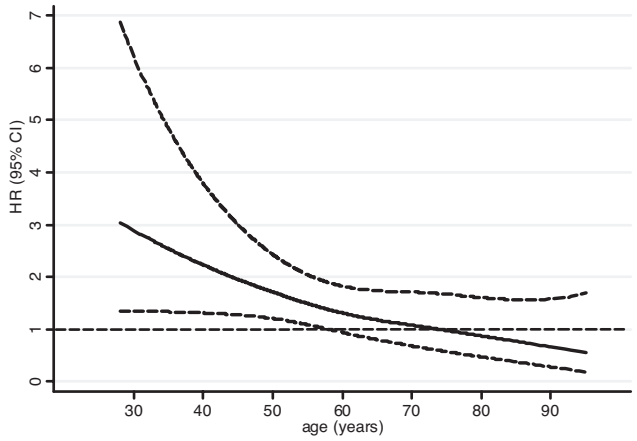

Figure 1. Hazard ratio (HR, solid line) and 95% CI (dashed lines) per 1-unit increase in mean bone loss score as a function of age.

Several causal and noncausal pathways have been postulated to explain the observed association between periodontitis (or other chronic infections) and CHD.[2,12] Causal pathways may involve direct and indirect effects of the periodontal infection,[12] whereas genetic and other host factors that increase the susceptibility to both atherosclerosis/thrombosis and chronic periodontitis would be an alternative noncausal pathway (Figure 2).

The epidemiological studies available today are not able to differentiate between these causal and noncausal pathways, even if they perfectly control for all established cardiovascular risk factors. Thus, both causal and noncausal pathways may have a role in the observed association (Figure 2).

Several cross-sectional studies suggest that periodontitis is associated with systemic markers of inflammation, including serum C-reactive protein[31,32] and plasma fibrinogen.[32,33] In addition, several uncontrolled and controlled intervention studies suggest that periodontal treatment may reduce inflammatory biomarkers such as C-reactive protein,[13] although results are equivocal.[34] In addition, a recent randomized controlled trial suggested that successful periodontal therapy may improve endothelial function.[14] Furthermore, bacterial DNA and viable periodontal pathogens have been isolated from human atheromas.[35] These results provide indirect evidence for a causal role of periodontitis in the pathogenesis of CHD via direct and indirect pathways (Figure 2). However, the relative importance of such causal mechanisms compared with confounding by common proinflammatory susceptibility factors is uncertain.

Tooth loss, and in particular complete tooth loss (edentulism), should reduce the increased risk for CHD associated with the causal effects of periodontitis by reducing or

Table 3. Association Between Periodontitis and Fatal Incident CHD for Men ≥60 Years of Age

	Median	Teeth Remaining, Median, n	Fatal CHD Events, n	Person-Years	HR (95% CI)*	HR (95% CI)†
MBLS						
0.5	0.31	26	6	2633	1.00	1.00
0.5–1	0.77	24	17	3937	1.63 (0.64–4.15)	1.48 (0.57–2.82)
1–1.5	1.22	21	17	3004	1.95 (0.76–4.98)	1.59 (0.61–4.15)
>1.5	1.88	15	14	1877	2.32 (0.88–6.15)	2.08 (0.77–5.62)
Edentulous		0	17	989	6.45 (2.50–16.6)	4.21 (1.57–11.3)
CPD						
<4 mm	0	22	15	3257	1.00	1.00
4–20 mm	12	22	20	3675	1.10 (0.56–2.15)	1.28 (0.63–2.62)
>20 mm	38	24	19	4442	0.84 (0.42–1.66)	1.09 (0.53–2.24)
Edentulous		0	17	989	3.58 (1.77–7.21)	2.97 (1.41–6.25)

MBLS indicates mean bone loss score; CPD, cumulative probing depth.

*Adjusted for age. Trend: MBLS, $P=0.05$; CPD, $P=0.20$.

†Adjusted for age, body mass index, high-density lipoprotein cholesterol, total cholesterol, triglycerides, hypertension, mean systolic and diastolic blood pressure, diabetes mellitus, fasting glucose, smoking, alcohol intake, occupation and education, income, and marital status. Trend: MBLS, $P=0.19$; CPD, $P=0.33$.

eliminating the exposure to periodontal inflammation. Indeed, a small uncontrolled study of 67 patients with advanced periodontitis suggested that serum concentrations of inflammatory biomarkers may decrease after full-mouth tooth extractions.[36] However, a large representative cross-sectional study of the US population found similar serum C-reactive protein concentrations in edentulous subjects as in subjects with chronic periodontitis.[31] Complete tooth loss may be a marker of previous periodontitis. The authors therefore suggested that the increased C-reactive protein concentrations among the edentulous may be a marker of a common underlying proinflammatory trait that may predispose to both CHD and periodontitis/tooth loss (Figure 2).[31] The present finding of a higher CHD incidence among older edentulous men than among older dentate men who were periodontally healthy is also consistent with this hypothesis. Edentulism may contribute to CHD risk through alternative pathways such as nutrition; however, dietary changes associated with tooth loss appear to be small, and their relevance for CHD risk is questionable.[37] Alternatively, edentulism may be a surrogate for socioeconomic status, and residual confounding may contribute to the observed association. For example, edentulism may in part reflect less long-term access to care that may have resulted in less effective treatment of cardiovascular risk factors, including hypertension, diabetes mellitus, and hyperlipidemia.

The finding that the association between periodontitis and CHD incidence is limited to younger men is consistent with previous studies,[1,21] and this modification of the effect of periodontitis by age is also a consistent finding in studies on ischemic stroke.[22,23] The present results suggest that the association decreases continuously with increasing age and

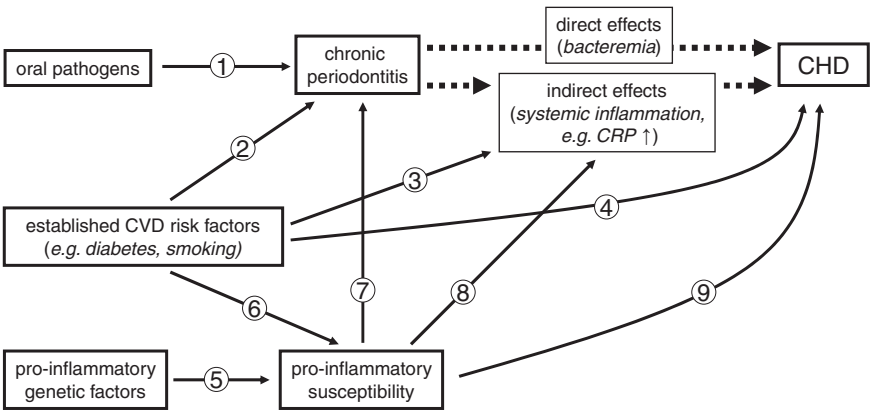

Figure 2. Possible pathways explaining the periodontitis–CHD association. The dotted arrows describe the causal association of interest, because chronic periodontitis may be a cause of cardiovascular disease through direct (bacteremia) and indirect (systemic inflammation) effects.[12] Oral bacteria are considered a necessary cause of chronic periodontitis (pathway 1).[25] Smoking is a strong environmental risk factor for chronic periodontitis (2)[26] and is also an important risk factor for cardiovascular disease (4), which may in part be mediated through its effect on systemic inflammation (3) (eg, elevated C-reactive protein [CRP] concentrations).[27] Common susceptibility to the inflammatory diseases, including periodontitis and cardiovascular disease, (7, 8, 9) is determined by genetic (5) and environmental factors, some of which may also be established cardiovascular risk factors (6). Evidence is compelling for a strong genetic base for both periodontitis[28] and cardiovascular disease,[29] some of which is likely mediated through inflammatory mechanisms (5). On the other hand, diabetes mellitus is an established cardiovascular risk factor that may increase the susceptibility to both periodontitis and cardiovascular disease through the increased formation of advanced glycosylation end products, which are proinflammatory (6).[30] Note that even with perfect adjustment for established cardiovascular risk factors such as smoking and diabetes mellitus, a common proinflammatory susceptibility (at least as far as determined by genetic factors) that predisposes to both periodontitis and CHD may confound the periodontitis–CHD association (noncausal pathway).

approaches the null at ≈60 to 65 years of age. Men with a higher susceptibility to periodontitis will exhibit a given degree of periodontal destruction at an earlier age than men with lower susceptibility to inflammatory periodontitis. In other words, periodontitis at a younger age is a marker of higher disease susceptibility. Therefore, the finding of a significant association between periodontitis and CHD incidence among young men, its continuous decrease with increasing age, and no association among older men in the present study is also consistent with the hypothesis that common proinflammatory susceptibility factors explain a large part of the observed association.

Treatment of periodontitis typically results in a reduction or elimination of periodontal pockets but does not typically result in a regeneration of lost bone. Hence, alveolar bone loss is a better measure of periodontitis history, although the cumulative pocket depth measure used in the present study is a better measure of current exposure to periodontal inflammation. Furthermore, the latter measure adequately accounts for the reduction in inflammatory exposure due to tooth loss.[33] This is also illustrated by the decrease in the number of remaining teeth across categories of mean bone loss score compared with the slight increase in the number of remaining teeth with increasing cumulative pocket depth (Table 2). Therefore, one would expect cumulative pocket depth to be a better clinical measure of periodontitis if the periodontal inflammation itself was a causal risk factor for CHD; however, in the present study, bone loss and pocket depth measures yielded similar results.

The ultimate question of whether periodontal treatment can reduce the risk of CHD can only be answered in a randomized controlled clinical trial. Recently, Tonetti et al[14] reported results from a randomized clinical trial indicating that periodontal treatment significantly improved endothelial function and other surrogate markers of CHD risk. However, the feasibility of a trial on true CHD end points may be questioned because both severe periodontitis and incident CHD are less common among younger persons, whereas the present and other epidemiological studies suggest that no association exists among older persons, in whom both conditions are more common.

The availability of repeated clinical and radiographic measures of periodontitis over a long follow-up period is an important strength of the present study compared with other available cohort studies. Furthermore, we were able to control for several important CHD risk factors and confounders using time-varying covariates. Some of the available cohort studies have been criticized for lack of adequate control for smoking.[5] We used a novel comprehensive smoking index that simultaneously accounts for intensity, duration, and time since cessation of smoking to minimize residual confounding.[20] In addition, sensitivity analyses restricted to never-smokers yielded consistent estimates (data not shown). However, residual confounding (in particular by dimensions of socioeconomic status not fully captured by the measures available in the present study[38] or due to changes in income not captured by our time-invariant measure) may still be a concern. This is particularly relevant for estimates of the effects of edentulism, because fully adjusted estimates were markedly attenuated compared with age-adjusted estimates.

Further limitations of the present study include its moderate sample size, which limited the precision of estimates. Hence, considerable uncertainty remains as to the strength of the association between periodontitis and CHD. Furthermore, the present cohort consisted almost exclusively of white men, and generalizability of these findings to other populations is uncertain.

In conclusion, the results of the present study suggest that chronic periodontitis is associated with incidence of CHD among younger men, independent of established cardiovascular risk factors. However, after complete tooth loss, risk for total and fatal CHD is elevated compared with periodontally healthy dentate older men. Although periodontitis may be a causal risk factor for CHD, the present results may suggest that an increased proinflammatory susceptibility common to both periodontitis and CHD may be important on a population level.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Chronic periodontitis is a highly prevalent inflammatory disease of the periodontium and an important cause of tooth loss. More recently, periodontitis has been implicated as a putative cardiovascular risk factor. We studied the association between periodontitis/edentulism and incident coronary heart disease (CHD) in the VA Normative Aging/Dental Longitudinal Study, an ongoing long-term closed-cohort study of men in the greater Boston (Massachusetts) area that performed comprehensive medical and dental examinations triennially. A total of 1203 men free of CHD at baseline were followed up for up to 35 years (median 24 years). Of these, a total of 364 men were diagnosed with CHD (either fatal or nonfatal), and 109 men died of CHD. We found a dose-dependent association between chronic periodontitis and incidence of CHD among men <60 years of age. Compared with men with no or minimal periodontal bone loss, men with severe periodontal bone loss had more than twice the risk of developing CHD (hazard ratio 2.12, 95% confidence interval 1.26 to 3.60). No association was found among men >60 years of age. Edentulous men ≥ 60 years of age tended to be more likely to develop any CHD and were significantly more likely to develop fatal CHD than dentate and periodontally healthy men. In summary, chronic periodontitis is associated with incident CHD among younger men.