Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 37, No. 2, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(00)01130-X

Periodontal Disease and Risk of Subsequent Cardiovascular Disease in U.S. Male Physicians

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OBJECTIVES We sought to prospectively assess whether self-reported periodontal disease is associated with subsequent risk of cardiovascular disease in a large population of male physicians.

BACKGROUND Periodontal disease, the result of a complex interplay of bacterial infection and chronic inflammation, has been suggested to be a predictor of cardiovascular disease.

METHODS Physicians' Health Study I was a randomized, double-blind, placebo-controlled trial of aspirin and beta-carotene in 22,071 U.S. male physicians. A total of 22,037 physicians provided self-reports of presence or absence of periodontal disease at study entry and were included in this analysis.

RESULTS A total of 2,653 physicians reported a personal history of periodontal disease at baseline. During an average of 12.3 years of follow-up, there were 797 nonfatal myocardial infarctions, 631 nonfatal strokes and 614 cardiovascular deaths. Thus, for each end point, the study had >90% power to detect a clinically important increased risk of 50%. In Cox proportional hazards regression analysis adjusted for age and treatment assignment, physicians who reported periodontal disease at baseline had slightly elevated, but statistically nonsignificant, relative risks (RR) of nonfatal myocardial infarction, (RR, 1.12; 95% confidence interval [CI], 0.92 to 1.36), nonfatal stroke (RR, 1.10; CI, 0.88 to 1.37) and cardiovascular death (RR, 1.20; CI, 0.97 to 1.49). Relative risk for a combined end point of all important cardiovascular events (first occurrence of nonfatal myocardial infarction, nonfatal stroke or cardiovascular death) was 1.13 (CI, 0.99 to 1.28). After adjustment for other cardiovascular risk factors, RRs were all attenuated and nonsignificant.

CONCLUSIONS These prospective data suggest that self-reported periodontal disease is not an independent predictor of subsequent cardiovascular disease in middle-aged to elderly men. (J Am Coll Cardiol 2001;37:445–50) © 2001 by the American College of Cardiology

Results of several cross-sectional (1,2) and case-control (3,4) studies have raised the possibility that persons with periodontal disease (gingivitis or periodontitis) may have increased risks of cardiovascular disease. Periodontal disease, which is caused by Gram-negative bacteria found in the oral flora, is common among adults in the U.S. Periodontal pockets and loss of attachment, the anatomical sequelae of periodontal disease, have been estimated to occur in 116 million Americans (5), while advanced destruction, as evidenced by pockets of ≥4 mm, is reported to occur in 28 million of those persons (5). Over time, the bacterial endotoxins in the mouth may enter the systemic circulation through gingival connective tissue and produce vascular injury. In view of the common occurrence of the condition, the demonstration of a role for periodontal disease in cardiovascular disease would have important public health implications.

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Manuscript received May 25, 2000; revised manuscript received September 12, 2000, accepted October 16, 2000.

There have been few prospective cohort studies of periodontal disease and risk of cardiovascular disease, and the data are inconsistent. A 14-year follow-up study of 9,760 participants in the National Health and Nutrition Epidemiologic Follow-Up Study indicated a small, but statistically significant, 25% increased risk of coronary heart disease (CHD) in persons with periodontal disease at baseline, compared to those with minimal disease, based on a periodontal score developed from a standard dental examination at baseline (6). Similarly, data from the Longitudinal Study of Aging suggested that persons with periodontal disease, based on an assessment of bone loss and probing pocket depth, had a 50% increased risk of CHD, compared to those without periodontal disease, during an 18-year follow-up period (7). However, a study of 44,119 male health professionals indicated no overall association between self-reported periodontal disease and CHD, although among those with preexisting periodontal disease, there was an inverse relationship between the reported number of teeth present and risks of subsequent CHD (8).

In this report, we examined the relationship between a report of periodontal disease and subsequent cardiovascular disease using prospective data from Physicians' Health Study I (PHS I), a randomized, double-blind, placebo-controlled trial of aspirin and beta-carotene in the prevention of cancer and cardiovascular disease among 22,071 U.S.

Abbreviations and Acronyms
CHD = coronary heart disease
PHS I = Physicians' Health Study I
RR = relative risk

male physicians. We also examined the relationship of reported tooth loss during follow-up with the risk of cardiovascular disease in the total population, and separately among those who did and did not report periodontal disease at baseline.

METHODS

Study population. A detailed description of the subjects and methods of PHS I has been presented elsewhere (9). Briefly, PHS I was a randomized, double-blind, placebo-controlled trial of aspirin and beta-carotene in the prevention of cancer and cardiovascular disease among 22,071 U.S. male physicians aged 40 to 84 years at entry in 1982. Participants were without a history of myocardial infarction, stroke, transient cerebral ischemia or cancer (except non-melanoma skin cancer). At baseline, study participants completed mailed questionnaires providing information on previous diagnoses of a range of diseases. Participants were asked "Do you have a personal history of any of the following?," with response options including periodontal disease. Baseline information was also collected on potential confounding variables including age, history of diabetes mellitus, current blood pressure level, history of high cholesterol level, height, weight, alcohol use, cigarette smoking, diuretic use, physical activity, multivitamin use and parental history of myocardial infarction. Subsequent annual questionnaires asked about adherence to treatments and the occurrence of study outcomes, including the number of teeth lost, since the previous questionnaire. Participants were asked "Since you filled out the last questionnaire (about 12 months ago), have you been newly diagnosed as having any of the following conditions?", with response options including periodontal disease and teeth loss in past year (If yes, how many).

Ascertainment and definition of end points. Following the report of a cardiovascular event, written consent for review of medical records was obtained and information was requested from hospitals and treating physicians. Reports of cardiovascular disease were considered refuted or confirmed only after the examination of all available information by an end points committee blinded to participants' periodontal disease status. Diagnoses of nonfatal myocardial infarction were confirmed with the use of World Health Organization criteria (10). Nonfatal stroke was defined as a typical neurologic deficit, either sudden or rapid in onset, that lasted >24 h and was attributed to a cerebrovascular event. Death due to a cardiovascular cause was confirmed by convincing evidence of a cardiovascular mechanism from all available sources, including death certificates, hospital records, and—for deaths outside the hospital—observers' impressions. Only confirmed end points were included in this analysis.

The present report includes data as of October 1995. By this date, participants had been followed up for an average of 12.3 years, morbidity follow-up was 99.7% complete and mortality follow-up was 100% complete. Records were available for review for 94.8% of all deaths. The available data provided power of over 0.9 to detect a clinically important 50% increased risk of each end point (nonfatal myocardial infarction, nonfatal stroke, cardiovascular death).

Data analysis. Rates of cardiovascular disease were calculated by dividing the number of cardiovascular events by person-time of follow-up in the periodontal disease and no periodontal disease groups. Cox proportional hazards regression models (11) were used to assess the independent contribution of a history of periodontal disease to the risk of cardiovascular disease. Separate analyses were conducted for the end points of nonfatal myocardial infarction, nonfatal stroke and cardiovascular death. For nonfatal myocardial infarction and nonfatal stroke, only the first confirmed event in each category was counted. We also examined the end point of all important cardiovascular events, a combined end point of first occurrence of nonfatal myocardial infarction or nonfatal stroke or cardiovascular death.

In initial regression analyses, relative risk (RR) estimates were obtained by controlling for the effects of age and aspirin and beta-carotene treatment assignment. To control for the effects of multiple potential confounders, multivariate models were also fit that included indicator terms for history of diabetes (yes/no), history of hypertension (systolic blood pressure of ≥160 mm Hg, diastolic blood pressure of ≥95 mm Hg, or history of treatment for high blood pressure) (yes/no), body mass index (continuous), cigarette smoking (never, past, current [<20/day, ≥20/day]), alcohol use (four categories), physical activity (reported vigorous exercise once/week or more) (yes/no), history of angina pectoris (yes/no) and parental history of myocardial infarction (yes/no). Interaction terms were used to examine possible modification of the association of periodontal disease and cardiovascular disease by baseline category of age (<60 years, ≥60 years), smoking (current, not current), alcohol (daily, less than daily), diabetes (yes/no), hypertension (yes/no), obesity (body mass index ≥27.8 kg/m^2) (yes/no) and aspirin assignment (active, placebo).

We also examined the association of cardiovascular disease with tooth loss reported during follow-up by modeling tooth loss as a time-varying covariate in separate proportional hazard models. Models were fit for the total population, and for those who did and did not report periodontal disease at baseline. For each RR, we calculated the two-sided p value and 95% confidence interval (12).

Table 1. Characteristics of Study Participants by Self-reported Periodontal Disease at Baseline in the Physicians' Health Study I

Characteristics	Periodontal Disease at Baseline	
	Yes (n = 2,653)	No (n = 19,384)
Mean age, yr	55.1	53.0
40–49	31.3	42.4
50–59	37.8	33.2
60–69	22.4	18.0
70+	8.5	6.4
Medical history		
Reported hypertension, %*	13.9	13.9
Reported diabetes mellitus, %	3.6	2.2
Mean body mass index, kg/m^2	25.0	24.9
History of angina pectoris, %	1.9	1.2
Parental history of MI, %†	13.7	13.0
Cigarette smoking		
Never, %	34.4	51.7
Past only, %	45.5	38.6
Current		
<20/d, %	6.0	3.6
≥20/d, %	14.1	6.2
Alcohol use		
Daily, %	28.9	24.3
Weekly, %	48.7	49.2
Physical activity, %‡	66.9	73.0

*Hypertension is defined as reported systolic blood pressure of ≥160 mm Hg, diastolic blood pressure of ≥95 mm Hg or history of treatment for high blood pressure. †Myocardial infarction (MI) in either parent before age 60 years. ‡Reported vigorous exercise at least once per week.

RESULTS

At baseline, 2,653 (12.0%) men reported a history of periodontal disease. These men were older and, after adjusting for age, reported more cigarette smoking, daily alcohol use, history of angina pectoris and diabetes, but less physical activity, than men who did not report periodontal disease at baseline (Table 1). Similar differences in baseline characteristics were noted when we compared men who did and did not report tooth loss during follow-up (data not shown).

During an average of 12.3 years of follow-up, there were 797 nonfatal myocardial infarctions, 631 nonfatal strokes and 614 cardiovascular deaths. In analyses adjusting for age and treatment assignment, men who reported periodontal disease at baseline, compared to those who did not, had slightly elevated, but statistically nonsignificant, increased risks of nonfatal myocardial infarction, nonfatal stroke and cardiovascular death (Table 2). For the combined end point of all important cardiovascular events, there was a statistically nonsignificant 13% increased risk for men who reported periodontal disease at baseline. After further adjustment for cigarette smoking and other possible cardiovascular risk factors, all RRs were attenuated and near the null value of 1.0. Tests of interaction with baseline variables indicated no important modification of the periodontal disease-cardiovascular disease association by these variables.

A total of 6,922 participants reported losing one or more teeth during the follow-up period. The results of multivariate analyses indicated that tooth loss during follow-up was not associated with risks of nonfatal myocardial infarction or nonfatal stroke (Table 3). However, against the a priori hypothesis, there was a statistically significant 39% decreased risk of cardiovascular death for those who reported tooth loss. Thus, the combined end point of all important cardiovascular events indicated an 8% lower risk for those with tooth loss that, nevertheless, was not statistically significant. The results were not materially different when analyses were conducted separately among those who did and did not report periodontal disease at baseline (Table 4).

DISCUSSION

In these prospective data from a large cohort of U.S. physicians, men who reported a history of periodontal disease at baseline, compared to those who reported no periodontal disease, had small (10% to 20%), and statistically nonsignificant, increased risks of nonfatal myocardial infarction, nonfatal stroke and cardiovascular death after adjustment for age and treatment assignment. However,

Table 2. Self-reported Periodontal Disease at Baseline and Relative Risk of Nonfatal Myocardial Infarction, Nonfatal Stroke, Cardiovascular Death and All Important Cardiovascular Events in the Physicians' Health Study I

End Point	Periodontal Disease at Baseline				Adjusted for Age and Treatment RR (95% CI)	Multivariate* RR (95% CI)
	Yes (n = 2,653)		No (n = 19,384)			
	N	%	N	%		
Nonfatal MI	115	4.3	682	3.5	1.12 (0.92–1.36)	1.01 (0.82–1.24)
Nonfatal stroke	94	3.5	537	2.8	1.10 (0.88–1.37)	1.01 (0.81–1.27)
CV death	100	3.8	514	2.7	1.20 (0.97–1.49)	1.00 (0.79–1.26)
All important CV events	275	10.4	1,555	8.0	1.13 (0.99–1.28)	1.01 (0.88–1.15)

*Adjusted for age (years), aspirin and beta-carotene treatment assignment, cigarette smoking, alcohol use, history of hypertension (systolic blood pressure of ≥160 mm Hg, diastolic blood pressure of ≥95 mm Hg or history of treatment for high blood pressure), body mass index, reported history of diabetes, physical activity (reported vigorous exercise once per week or more), parental history of myocardial infarction and history of angina.

CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; RR = relative risk.

Table 3. Self-reported Tooth Loss During Follow-up and Relative Risk of Nonfatal Myocardial Infarction, Nonfatal Stroke, Cardiovascular Death and All Important Cardiovascular Events in the Physicians' Health Study I

	Tooth Loss During Follow-up					
	Yes (n = 6,922)		No (n = 15,115)		Adjusted for Age and Treatment	Multivariate*
End Point	N	%	N	%	RR (95% CI)	RR (95% CI)
Nonfatal MI	326	4.7	471	3.1	1.12 (0.97–1.30)	1.01 (0.87–1.17)
Nonfatal stroke	289	4.2	342	2.3	1.14 (0.97–1.34)	1.07 (0.91–1.27)
CV death	209	3.0	405	2.7	0.63 (0.53–0.75)	0.61 (0.51–0.73)
All important CV events	744	10.8	1,086	7.2	0.98 (0.89–1.08)	0.92 (0.83–1.01)

*Adjusted for age (years), aspirin and beta-carotene treatment assignment, cigarette smoking, alcohol use, history of hypertension (systolic blood pressure of ≥160 mm Hg, diastolic blood pressure of ≥95 mm Hg or history of treatment for high blood pressure), body mass index, reported diabetes at baseline, physical activity (reported vigorous exercise once per week or more), parental history of myocardial infarction and history of angina.
CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; RR = relative risk.

with further adjustment for cigarette smoking and other possible cardiovascular risk factors, estimates were reduced to the null value of 1.0. Reported tooth loss during follow-up was not associated with risks of nonfatal myocardial infarction or nonfatal stroke, but there was an unexpected and statistically significant 39% reduced risk of cardiovascular death for those who reported tooth loss, an apparent inverse association that goes against the a priori hypothesis. Thus, these results do not support the hypothesis that periodontal disease is an independent predictor of cardiovascular disease.

Previous studies. There have been few previous prospective studies of periodontal disease and CHD, and the data are inconsistent. A study of 9,760 adult participants in the National Health and Nutrition Epidemiologic Follow-up Study indicated a small, but statistically significant, 25% increased risk of CHD in persons with periodontal disease at baseline, compared to those with minimal periodontal disease, after a median follow-up of 14 years (6). A similar size increase in risk of CHD was also reported for persons with complete tooth loss at baseline in that study. However, information on cigarette smoking, a potentially important confounder of these associations, was available only for a subsample of the study population. A second prospective study, based on combined data for 1,147 participants in the Normative Aging Study and the Dental Longitudinal Study, also indicated an association of periodontal disease and CHD. Analyses conducted after an average of 18 years

Table 4. Self-reported Tooth Loss During Follow-up and Relative Risk of Nonfatal Myocardial Infarction, Nonfatal Stroke, Cardiovascular Death and All Important Cardiovascular Events According to Self-reported Periodontal Disease at Baseline in the Physicians' Health Study I

Periodontal Disease at Baseline

	Tooth Loss During Follow-up					
	Yes (n = 1,468)		No (n = 1,185)		Adjusted for Age and Treatment	Multivariate*
End Point	N	%	N	%	RR (95% CI)	RR (95% CI)
Nonfatal MI	76	5.2	39	3.3	1.45 (0.98–2.14)	1.21 (0.80–1.83)
Nonfatal stroke	64	4.4	30	2.5	1.23 (0.79–1.89)	1.20 (0.76–1.89)
CV death	51	3.5	49	4.1	0.58 (0.39–0.87)	0.64 (0.41–0.99)
All important CV events	172	11.7	103	8.7	1.06 (0.83–1.35)	1.01 (0.77–1.31)

No Periodontal Disease at Baseline

	Tooth Loss During Follow-up					
	Yes (n = 5,454)		No (n = 13,930)		Adjusted for Age and Treatment	Multivariate*
End Point	N	%	N	%	RR (95% CI)	RR (95% CI)
Nonfatal MI	250	4.6	432	3.1	1.06 (0.90–1.24)	0.97 (0.82–1.15)
Nonfatal stroke	225	4.1	312	2.2	1.12 (0.93–1.33)	1.05 (0.88–1.27)
CV death	158	2.9	356	2.6	0.61 (0.51–0.76)	0.60 (0.49–0.73)
All important CV events	572	10.5	983	7.1	0.95 (0.85–1.06)	0.90 (0.80–1.00)

*Adjusted for age (years), aspirin and beta-carotene treatment assignment, cigarette smoking, alcohol use, history of hypertension (systolic blood pressure of ≥160 mm Hg, diastolic blood pressure of ≥95 mm Hg or history of treatment for high blood pressure), body mass index, reported diabetes at baseline, physical activity (reported vigorous exercise once per week or more), parental history of myocardial infarction and history of angina.
CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; RR = relative risk.

of follow-up showed that individuals with high alveolar bone loss at baseline (defined as >20% whole mouth bone loss) had a statistically significant 50% increased risk of developing heart disease after controlling for age, body mass index, systolic blood pressure, cholesterol level and diabetes (7). There was also an approximate twofold increase in risk of fatal CHD (controlling for age, smoking, systolic blood pressure, diabetes) and a threefold increase in risk of stroke (controlling for age, smoking, diastolic blood pressure, diabetes, family history of heart disease, education) associated with high alveolar bone loss at baseline. However, the lack of detailed information on cigarette smoking (current smokers were defined as men who smoked one or more cigarettes daily) raises the possibility that residual confounding by smoking (and perhaps other risk factors) may have contributed to the findings of this study. Finally, no association was observed between self-reported periodontal disease and subsequent CHD in a six-year follow-up study of 44,119 male health professionals (8). Among men who reported pre-existing periodontal disease, however, men with ≤10 teeth at the beginning of follow-up, compared with men with ≥25 teeth, had an almost 70% increased risk of CHD.

Comparison between this and other studies. Our findings in a population of male physicians appear to agree with the results from the male health professionals study in indicating no association between self-reported periodontal disease and risk of cardiovascular disease. Our findings regarding tooth loss, however, appear to conflict with those from the male health professionals. This apparent discrepancy may be related to the way in which tooth loss was defined in the two populations. In the male health professionals study, tooth loss was defined as the reported number of teeth at baseline, and the authors suggest that tooth loss among participants who also reported periodontal disease may be a marker of severe periodontal disease. In PHS I, we did not ask about number of teeth at baseline, but instead requested study participants to report new tooth loss (within the past year) on each of the annual follow-up questionnaires. Thus, a report of recent tooth loss in our study may have been a marker of comparatively good health; that is, a participant willing to undergo elective procedures. The additional observation that the reduction in risk of death was greater in older (≥60 years) than in younger (<60 years) men who reported tooth loss (RRs 0.55 vs 0.73, respectively) appears consistent with this possibility. Alternatively, our unexpected finding of a reduced risk of cardiovascular death for those who reported tooth loss may simply have been a chance observation.

Possible study limitations. Several limitations of the study need to be considered. Because we did not conduct oral examinations of study participants, but instead relied on participant reports of periodontal disease (medical records to confirm the reports were not requested), some reports of periodontal disease may have been in error, and some true cases of periodontal disease may have been missed. The reported prevalence of periodontal disease at baseline in PHS I (12%) appears lower than that reported for other populations and may reflect some degree of underascertainment of disease. For example, the U.S. Public Health Service reported that 5% to 20% of the population suffer from severe generalized periodontal disease, and men are more likely to be affected than are women (5).

Misclassification of participants' periodontal disease status that was random with respect to subsequent cardiovascular disease would have biased the estimates toward the null, and may have contributed to our null findings. It seems unlikely, however, that the magnitude of random misclassification in our study would have been sufficient to cause us to miss a twofold to threefold increased risk of cardiovascular disease reported in several earlier studies. Although we did not validate the self-reports, a previous validation study conducted among dentists indicated reasonable predictive values for reported periodontal disease (predictive value positive, 0.76; predictive value negative, 0.74), with an expected attenuation of estimates of approximately 30% (13). Among nondentists in that study, self-reports of periodontal disease showed validity by confirmation of known associations with age and cigarette smoking. Although the degree of misclassification of self-reported periodontal disease in PHS I is likely to be somewhat higher than that observed in dentists, we similarly noted associations of reported periodontal disease with age and cigarette smoking, thus providing support for the validity of this measure in our study of male physicians. Misclassification of cardiovascular disease was unlikely in our study because of the use of strict criteria to define cardiovascular end points. Potential bias due to unavailability for follow-up was minimized by the high follow-up rate in PHS I. As of October 1995, 99.7% were still providing information on morbidity, follow-up for mortality was 100% complete and records were available for review for 94.8% of all deaths.

Although the idea that oral disease might have an effect on certain aspects of general health is not new, it has recently received renewed interest in the dental scientific community. The most plausible theory for an association remains the suggestion that infections and infectious agents found in the oral cavity could cause chronic inflammation, changes in platelet aggregation and other events associated with cardiovascular disease (14). The results from a population of physicians presented herein, however, suggest that self-reported periodontal disease may not be an independent risk factor for cardiovascular disease.

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