American Journal of Epidemiology
Vol. 151, No. 3

Examination of the Relation between Periodontal Health Status and Cardiovascular Risk Factors: Serum Total and High Density Lipoprotein Cholesterol, C-reactive Protein, and Plasma Fibrinogen

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Using data from the Third National Health and Nutrition Examination Survey (1988–1994), the authors examined the relation between periodontal health and cardiovascular risk factors: serum total and high density lipoprotein cholesterol, C-reactive protein, and plasma fibrinogen. A total of 10,146 participants were included in the analyses of cholesterol and C-reactive protein and 4,461 in the analyses of fibrinogen. Periodontal health indicators included the gingival bleeding index, calculus index, and periodontal disease status (defined by pocket depth and attachment loss). While cholesterol and fibrinogen were analyzed as continuous variables, C-reactive protein was dichotomized into two levels. The results show a significant relation between indicators of poor periodontal status and increased C-reactive protein and fibrinogen. The association between periodontal status and total cholesterol level is much weaker. No consistent association between periodontal status and high density lipoprotein cholesterol was detectable. Similar patterns of association were observed for participants aged 17–54 years and those 55 years and older. In conclusion, this study suggests that total cholesterol, C-reactive protein, and fibrinogen are possible intermediate factors that may link periodontal disease to elevated cardiovascular risk. *Am J Epidemiol* 2000;151:273–82.

cholesterol; C-reactive protein; fibrinogen; nutrition surveys; periodontitis

Periodontal disease, caused mainly by bacteria, is characterized by inflammation and destruction of the attachment apparatus of the teeth and affects a large number of the adult population in the United States (1, 2). The disease is classified into gingivitis and periodontitis. Gingivitis is manifested by red, swollen gums and bleeding that may occur with toothbrushing or gentle probing. Periodontitis is characterized by inflammatory destruction of the alveolar bone as well as loss of the soft tissue attachment to the teeth. Once initiated, periodontal disease maintains a slowly progressive and destructive character with periods of exacerbation and remission (3).

The role of periodontal disease in the etiology of cardiovascular disease (CVD) has recently received considerable attention. Several observational epidemiologic studies (4–12) have found that poor periodontal health status is associated with an increased risk for CVD. For example, DeStefano et al. (4), using 15-year follow-up data from the First National Health and Nutritional Examination Survey (NHANES I) Epidemiologic Followup Study, found that people with periodontitis had a 25 percent increased risk for coronary heart disease (CHD) relative to those with minimal periodontal disease after adjustment for age, sex, race, education, poverty index, marital status, systolic blood pressure, total cholesterol concentration, diabetes, body mass index, and alcohol consumption. A longitudinal study conducted by Beck et al. (5) found that the odds ratios were 1.5 for total CHD and 1.9 for fatal CHD among people with periodontal bone loss compared with those without bone loss, after adjusting for several risk factors for CVD.

Elevated inflammatory and homeostatic responses as well as lipid metabolism disturbance due to periodontal infection might be possible pathways underlying the observed association between periodontal disease and the increased risk for CVD (5, 13–15). However, few studies have examined these potential pathways. The purpose of this study is to examine the associations between periodontal status and a number of CVD risk factors (serum total and high density lipoprotein cho-

Received for publication November 16, 1998, and accepted for publication May 6, 1999.

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HDL cholesterol, high density lipoprotein cholesterol; NHANES III, Third National Health and Nutrition Examination Survey.

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lesterol (HDL cholesterol), C-reactive protein, and plasma fibrinogen) using data from a representative sample of the US population.

MATERIALS AND METHODS

Data and study sample

Data from the Third National Health and Nutrition Examination Survey (NHANES III) were used for this cross-sectional study. NHANES III was conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention. Using a stratified multistage probability sampling design, the National Center for Health Statistics collected data representing the total civilian, noninstitutionalized population, 2 months of age or over, in the 50 states and District of Columbia. NHANES III data collection was divided into two phases conducted from October 18, 1988, through October 15, 1994. The data set for each phase is nationally representative as is the sample including all 6 years. There were 39,695 persons selected over the 6 years; of those, 33,994 (86 percent) were interviewed in their homes. Seventy-eight percent (30,818 persons) of the selected persons were examined in the Mobile Examination Center, and an additional 493 persons were examined in their homes. More detailed information on the sample design and operation of NHANES III can be found elsewhere (16, 17).

The dependent variables used in this study include serum total and HDL cholesterol, C-reactive protein, and plasma fibrinogen. Detailed specimen collection and processing instructions are discussed in the NHANES III *Manual for Medical Technicians* (17). The analytical methods used by the participating laboratories are described in *Laboratory Procedures Used for NHANES III* (17). Relevant information is briefly summarized here.

Blood specimens were collected on those aged 1 year and older at the Mobile Examination Center or home. Immediately after specimen collection, vials were stored under appropriate conditions, refrigerated (4–8°C), or frozen (–20°C) until they were shipped to analytical laboratories for testing. Serum cholesterol analysis (18) was performed for participants aged 4 years and older, and plasma fibrinogen was tested for those aged 40 years and older.

C-reactive protein was quantified by latex-enhanced nephelometry. If lower than 0.3 mg/dl, the value of the C-reactive protein concentration was reported as <0.3 mg/dl. Seventy percent of the people in the data of our analyses have C-reactive protein concentrations lower than 0.3 mg/dl. Thus, for study purposes, C-reactive protein was categorized into two groups (low and high) according to the value of the 75th percentile of its distribution. Thus, C-reactive protein concentrations equal to or higher than 0.4 mg/dl were defined as elevated C-reactive protein levels.

Periodontal assessments include assessments of gingival bleeding, calculus, periodontal pocket depth, and periodontal attachment loss. The diagnostic criteria for these periodontal assessments were based on several references (19–21) that have also been used in several other national surveys.

Periodontal assessments were performed for NHANES III participants aged 13 years and older. One upper quadrant and one lower quadrant of the mouth were randomly selected for assessment. Buccal and mesiobuccal sites of the two quadrants were assessed. These assessments had been extensively field tested before NHANES III. The protocol for measuring each component can be found in the *Oral Examination Component Manual* (17).

Briefly, a standard periodontal probe was used to measure gingival bleeding and periodontal destruction for the buccal and mesiobuccal sites. Results of the gingival bleeding assessment for each site were categorized into either bleeding or no bleeding after gentle probing. Periodontal pocket depth, the distance in millimeters from the free gingival margin to the bottom of the pocket, and periodontal attachment loss, the distance in millimeters from the cemento-enamel junction to the bottom of the pocket, also were measured for each site.

Calculus was assessed for each of the buccal and mesiobuccal sites and categorized into one of three groups: absence of calculus (coded as 0), presence of supragingival but no subgingival calculus (coded as 1), and presence of subgingival calculus only or presence of both supragingival and subgingival calculus (coded as 2).

Gingival bleeding and calculus indices were calculated to summarize results of all tooth-site assessments for each individual. The percentage of teeth with gingival bleeding among all teeth examined was used to represent gingival bleeding status and named the gingival bleeding index. Specifically, a tooth with gingival bleeding was defined if either of the two tooth sites was assessed as bleeding. The arithmetic average of calculus scores for all tooth assessments was computed as the calculus index. Prior to the calculation of the calculus index, the two site assessments from each tooth were averaged. If only one site assessment was available, that one assessment was used for that tooth. The arithmetic average of calculus for all examined teeth was the calculus index used to summarize each individual's calculus status.

For study purposes, each index was categorized into three levels. The gingival bleeding index was categorized into 1) no bleeding (gingival bleeding index = 0),

2) mild bleeding (gingival bleeding index from 0.01 to 0.24), and 3) bleeding (gingival bleeding index from 0.25 to 1.00). The calculus index was categorized into 1) from 0 to 0.24, 2) from 0.25 to 0.74, and 3) from 0.75 to 2.00, with higher scores indicating more calculus.

Although lacking uniform criteria, the diagnosis of periodontitis is currently based on assessments of pocket depth and/or attachment loss of individual teeth (22). In this study, periodontal disease status also was defined according to the severity of periodontal pocket depth and attachment loss for individual teeth. As mentioned earlier, buccal and mesiobuccal sites of each tooth were assessed, and the two-site assessments were averaged to represent the measurement for the tooth. When only one site was assessed, that value was used instead of the average of the two sites. The three categories for periodontal disease status were 1) no disease, no tooth examined with pocket depth ≥2 mm or attachment loss ≥3 mm; 2) mild periodontitis, at least one examined tooth with pocket depth ≥2 mm or attachment loss ≥3; and 3) periodontitis, at least one examined tooth with pocket depth ≥3 mm or attachment loss ≥4 mm.

Household interviews and examinations at the Mobile Examination Center or participants' homes provided demographic information, medical history, health-related behaviors, and medical examination results. These data were used as covariates to control for potential confounding.

Demographic variables included sex, ethnicity (non-Hispanic White, non-Hispanic Black, Mexican, and other), number of years of education completed, age at examination, family size, and the poverty index.

The poverty index was computed as a ratio of two components. The numerator was the midpoint of the family income category reported by the participant. The denominator was the poverty threshold value produced annually by the Census Bureau. The threshold values are based on calendar years and adjusted for changes caused by inflation between calendar years. A value below one indicates that the family income is below the poverty threshold.

Diabetes status (yes/no) was obtained in the interview by asking, "Have you ever been told by a doctor that you have diabetes or sugar diabetes?" A family history of heart attack (yes/no) was obtained as part of the interview and referred to whether the mother, father, grandmother, grandfather, sister, brother, aunt, uncle, or cousin had a heart attack before age 50.

The health-related behaviors queried included tobacco use and alcohol consumption. The average number of cigarettes per day smoked currently, exsmoker status (yes/no), and whether ever chewed tobacco (yes/no) were included in the analyses. Information on alcohol consumption in average number of drinks per day during the past 12 months was also used.

Weight and height were measured during a physical examination (17). The body mass index was calculated from weight and height using the equation: body mass index = weight (kg)/height $(m)^2$.

The selection of samples for this study is shown in table 1. The total number selected for NHANES III was 39,695. Of those, 33,994 (86 percent) were interviewed, and 31,311 (79 percent) were examined. This study was limited to adult participants aged 17 and older: 20,050 adults were interviewed and 18,162 examined. A total of 16,427 adults received assessment for gingival bleeding, 14,017 for calculus, and 13,994 for periodontal pocket depth and attachment loss.

In order to improve the reliability of periodontal assessments, the sample used in this analysis was restricted to participants who had at least six teeth examined. After exclusion of those not meeting this criterion, 12,808 subjects remained. The sample size was further reduced to 10,800 because of exclusion of individuals with missing information on the covariates of interest.

Plasma fibrinogen was assessed only in a subset of NHANES III participants who were 40 years of age and older. As a result, the final sample size varied from 10,146 for the analyses of cholesterol and C-reactive protein to 4,461 for fibrinogen.

TABLE 1. Selection of study samples, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994

	Total	Adults (age 17 and older)
NHANES III sample size	39,695	
No. of participants interviewed	33,994	20,050
No. of participants examined	31,311	18,162
▼		
No. of participants with peridontal assessments (with ≥6 teeth examined)		
Gingival bleeding		15,268
Calculus		12,849
Pocket depth and attachment loss		12,822
≥6 teeth examined for each of the assessments		12,808
▼		
No. of participants with information on all covariates of interest		10,800
▼		
No. of participants with the following outcome measurements		
Serum cholesterol and C-reactive protein (ages 17 and older)		10,146
Plasma fibrinogen (ages 40 and older)		4,461

Statistical analysis

Descriptive statistics including means, standard deviations, and percentages were used to summarize the demographic variables and health-related behaviors of the study samples.

Mean values of total and HDL cholesterol and fibrinogen were compared between different categories of each periodontal measurement. In each comparison, the group with the minimal level of periodontal measurement scores or the minimal level of periodontal disease status was used as the referent group. Multiple linear regression was used to adjust for all covariates of interest in testing the differences in means.

Logistic regression analyses were used to examine the association between periodontal status and C-reactive protein. Odds ratios of a C-reactive protein concentration ≥0.4 mg/dl for people with poorer levels of periodontal measurement scores compared with those with a minimal level of periodontal measurement scores were derived after adjustment for all covariates of interest.

The gingival bleeding index, calculus index, and periodontal disease status (0 for no disease, 1 for mild periodontitis, and 2 for periodontitis) also were analyzed as continuous variables in the linear and the logistic regression models with CVD risk factors as dependent variables and with adjustment for all covariates. The regression coefficient for each periodontal health indicator was tested for statistical significance.

Previous studies have indicated that the association between poor periodontal status and an increased risk for CHD may be weaker in elderly compared with younger individuals (4, 9). In order to analyze whether the association between periodontal status and CVD risk factors varies with age, we performed analyses for the samples as a whole and separately for people aged 17–54 years and those aged 55 years and older.

As mentioned before, NHANES III used a complex sampling design, which needs to be taken into consideration in data analyses (23). Weights and primary sampling units and strata were available from the NHANES III data sets to facilitate analyses with adjustment for the design feature. Thus, linear and logistic regression analyses were performed with application of the weights and adjustment for the design feature. All analyses were performed using SUDAAN software (24).

RESULTS

Characteristics of the study samples are presented in table 2. Participants with fibrinogen (sample 2) information on average were older (weighted mean age, 53.5 years vs. 38.9 years), had a higher body mass index (27.3 vs. 26.2), and had a higher prevalence of diabetes (5.8 percent vs. 3.4 percent) compared with participants (sample 1) for the analyses of cholesterol and C-reactive protein. This difference is expected because, as mentioned in Materials and Methods, only those aged 40 years and older were selected for fibrinogen assessment.

Table 3 presents the average serum cholesterol (weighted and adjusted for all covariates of interest) for the referent category of each periodontal health indicator (i.e., gingival bleeding index, calculus index,

TABLE 2. Characteristics of study samples, Third National Health and Nutrition Examination Survey, 1988–1994

	Sample 1* (*n* = 10,146)		Sample 2† (*n* = 4,461)	
	Unweighted	Weighted	Unweighted	Weighted
	Percentage			
Female	53.1	50.8	50.8	51.0
Family history of heart attack	13.7	17.6	12.4	15.3
Diabetes	5.3	3.4	9.5	5.8
Ever chewing tobacco	7.2	10.0	7.6	7.5
Exsmoker	20.8	22.7	31.6	34.0
	Mean (standard deviation)			
Age (years)	40.37 (17.28)	38.86	56.42 (12.68)	53.52
Years of schooling (no.)	11.45 (3.62)	12.79	11.08 (4.27)	12.90
Family size (no.)	3.49 (1.98)	3.11	3.00 (1.79)	2.77
Poverty index	2.45 (1.79)	3.18	2.91 (1.96)	3.73
Body mass index (kg/m²)	26.94 (5.87)	26.22	27.95 (5.62)	27.25
Average alcohol use (drinks/day)	0.50 (1.19)	0.55	0.46 (1.12)	0.50
Average cigarettes smoked per day (no.)	3.55 (8.35)	4.94	3.35 (8.49)	4.13

* Sample 1: sample used for the analyses of serum cholesterol and C-reactive protein.
† Sample 2: sample used for the analyses of plasma fibrinogen.

TABLE 3. Differences in means and regression coefficients for serum total cholesterol (mg/dl) by periodontal health status, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994

	Age 17–54			Age ≥55			Total		
	Sample size (no.)	Mean†	Difference/ β‡	Sample size (no.)	Mean†	Difference/ β	Sample size (no.)	Mean†	Difference/ β
Gingival bleeding index									
Categorical									
0	3,348	191.28	0.00 (referent)	956	220.52	0.00 (referent)	4,304	196.62	0.00 (referent)
0.01–0.24	2,693		2.12 (1.14)§	716		3.54 (2.14)	3,409		2.08 (1.02)*
0.25–1.00	1,864		4.25 (2.21)	569		1.39 (3.43)	2,433		3.22 (2.09)
Continuous	7,905		7.30 (4.66)	2,241		4.28 (6.24)	10,146		5.97 (4.23)
Calculus index									
Categorical									
0–0.24	2,597	191.22	0.00 (referent)	584	219.13	0.00 (referent)	3,181	196.16	0.00 (referent)
0.25–0.74	2,732		2.43 (1.35)	715		4.71 (2.20)*	3,447		2.75 (1.23)*
0.75–2.00	2,576		2.35 (1.62)	942		3.10 (2.66)	3,518		2.51 (1.39)
Continuous	7,905		1.50 (1.23)	2,241		1.28 (2.23)	10,146		1.60 (0.95)
Periodontal disease (PD) status¶									
Categorical									
Non-PD	1,415	190.35	0.00 (referent)	272	219.75	0.00 (referent)	1,687	195.49	0.00 (referent)
Mild PD	4,238		2.82 (1.70)	925		4.10 (3.10)	5,163		2.98 (1.51)
PD	2,252		3.38 (2.08)	1,044		4.29 (3.41)	3,296		2.97 (1.85)
Continuous	7,905		1.68 (0.98)	2,241		0.70 (1.37)	10,146		1.21 (0.86)

* $p < 0.05$; ** $p < 0.01$.

† SUDAAN software and weights provided in NHANES III data were used, and age, ethnicity, education, sex, family size, poverty index, body mass index, family history of heart attack, diabetes status, smoking, chewing tobacco, and alcohol use were adjusted for using multiple linear regression. Mean total cholesterol was calculated from the regressions using mean values of all covariates.

‡ β, regression coefficient for the continuous variable of periodontal health status; referent, referent group in comparison of differences in means.

§ Numbers in parentheses, standard error.

¶ Non-PD, no tooth with pocket depth ≥2 mm or attachment loss ≥3 mm; mild PD, at least one tooth with pocket depth ≥2 mm or attachment loss ≥3 mm; PD, at least one tooth with pocket depth ≥3 mm or attachment loss ≥4 mm.

and periodontal disease status) and the differences in mean cholesterol levels for each category of a periodontal health indicator. Compared with its referent group, poorer periodontal status tended to be associated with an increase in total cholesterol concentration in the sample as a whole. In the age-specific groups, however, most of the differences did not reach statistical significance. When analyzed as continuous variables, each indicator of periodontal health had positive regression coefficients, indicating that poorer periodontal status might be associated with an increased total cholesterol concentration. However, none of the regression coefficients reached statistical significance.

For the comparison of HDL cholesterol (table 4), we found no significant difference in means for gingival bleeding, the calculus index, or periodontal disease status in any of the age-specific groups or in the sample as a whole. Furthermore, no significant association was detectable for any of the periodontal health indicators when they were analyzed as continuous variables.

We found a consistent and significant association between periodontal health indicators (gingival bleeding index and calculus in particular) and C-reactive protein (table 5). For example, when analyzed as a continuous variable, each of the three periodontal health indicators was significantly associated with increased C-reactive protein (≥0.4 mg/dl) in the sample as a whole. The direction of the estimated association between each periodontal indicator and C-reactive protein is consistent for participants aged 17–54 years and those aged 55 years and older. However, for the older group, none of the estimates reached statistical significance.

Results for plasma fibrinogen are shown in table 6. For the gingival bleeding index, no significant association was observed in the age-specific groups or the sample as a whole. For the calculus index, there was a significant and positive association of increasing fibrinogen with increasing calculus in those aged 17–54 years and in the sample as a whole. An increase in fibrinogen associated with a poorer calculus level tended to be larger for those aged 17–54 years compared with that for those aged 55 years and older. For periodontal disease status, analyzed as a continuous variable, a significant association with

TABLE 4. Difference in means and regression coefficients for serum high density lipoprotein cholesterol (HDL cholesterol) (mg/dl) by periodontal health status, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994

	Age 17–54			Age ≥55			Total		
	Sample size (no.)	Mean†	Difference/ β‡	Sample size (no.)	Mean†	Difference/ β	Sample size (no.)	Mean†	Difference/ β
Gingival bleeding index									
Categorical									
0	3,348	51.31	0.00 (referent)	956	53.58	0.00 (referent)	4,304	51.66	0.00 (referent)
0.01–0.24	2,693		−0.57 (0.59)§	716		0.49 (1.18)	3,409		−0.44 (0.52)
0.25–1.00	1,864		0.19 (0.71)	569		−2.15 (1.56)	2,433		−0.27 (0.63)
Continuous	7,905		0.89 (1.28)	2,241		−3.65 (3.03)	10,146		0.08 (1.18)
Calculus index									
Categorical									
0–0.24	2,597	51.37	0.00 (referent)	584	53.90	0.00 (referent)	3,181	51.80	0.00 (referent)
0.25–0.74	2,732		0.02 (0.55)	715		−1.27 (1.49)	3,447		−0.28 (0.47)
0.75–2.00	2,576		−0.86 (0.65)	942		−0.35 (1.35)	3,518		−0.80 (0.57)
Continuous	7,905		−0.76 (0.56)	2,241		−0.78 (0.94)	10,146		−0.75 (0.46)
Periodontal disease (PD) status¶									
Categorical									
Non-PD	1,415	50.98	0.00 (referent)	272	53.71	0.00 (referent)	1,687	51.40	0.00 (referent)
Mild PD	4,238		0.31 (0.72)	925		−0.51 (1.29)	5,163		0.14 (0.62)
PD	2,252		−0.05 (0.84)	1,044		−0.44 (1.75)	3,296		−0.06 (0.71)
Continuous	7,905		−0.04 (0.43)	2,241		−0.08 (0.71)	10,146		−0.02 (0.34)

* $p < 0.05$; ** $p < 0.01$.

† SUDAAN software and weights provided in NHANES III data were used, and age, ethnicity, education, sex, family size, poverty index, body mass index, family history of heart attack, diabetes status, smoking, chewing tobacco, and alcohol use were adjusted for using multiple linear regression. Mean HDL cholesterol was calculated from the regressions using mean values of all covariates.

‡ β, regression coefficient for the continuous variable of periodontal health status; referent, referent group in comparison of differences in means.

§ Numbers in parentheses, standard error.

¶ Non-PD, no tooth with pocket depth ≥2 mm or attachment loss ≥3 mm; mild PD, at least one tooth with pocket depth ≥2 mm or attachment loss ≥3 mm; PD, at least one tooth with pocket depth ≥3 mm or attachment loss ≥4 mm.

fibrinogen was observed only in the sample as a whole.

To show the appropriateness of the regression models, the relation of the covariates of interest with C-reactive protein and fibrinogen is presented in table 7. As expected, age, female sex, body mass index, and cigarette smoking are associated positively with both C-reactive protein and fibrinogen.

DISCUSSION

These cross-sectional analyses of the data from a sample representative for the US population support the existence of a significant relation between periodontal health status and both C-reactive protein and fibrinogen. The association between periodontal status and the total cholesterol level tends to be weaker if not nonsignificant. No consistent association between periodontal status and HDL cholesterol was detectable. The directions of the estimates are generally consistent for participants aged 17–54 years and those aged 55 years and older.

The observed associations are supported by a number of potential pathophysiologic links. Periodontal disease could result in repeated systematic exposures to bacteria, endotoxin lipopolysaccharide, and other bacterial products that may influence lipid metabolism and homeostasis. The gingival sulcus may harbor as much as 200 mg of plaque that consists of a large number of microorganisms that can directly invade the periodontal tissue (25). The loss of epithelial integrity within the periodontal pocket also creates an opportunity for direct bacterial translocation and bacteremia. Oral bacteria have been found circulating in the blood following toothbrushing, dental extraction, and periodontal surgery (26). The more severe the periodontal inflammation, the greater the hematogenous bacterial exposure in terms of bacterial counts and duration (27–29). In addition, the lipopolysaccharide of dental plaque can penetrate the gingiva and elicit a systemic lipopolysaccharide-specific antibody response (30, 31).

Systematic exposure to oral bacteria may lead to lipid metabolism disturbance and a hypercoagulable state through elevating circulating cytokines. Previous studies suggest that lipopolysaccharide acts as a systemic trigger that can activate an impressive cascade of inflammatory cytokines eliciting most of the vascular

TABLE 5. Odds ratios of C-reactive protein elevation (serum C-reactive protein ≥0.4 mg/dl) for different levels of periodontal health status, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994

	Age 17–54			Age ≥55			Total		
	Sample size (no.)	OR†,‡	95% CI†	Sample size (no.)	OR‡	95% CI	Sample size (no.)	OR‡	95% CI
Gingival bleeding index									
Categorical									
0	3,348	1.00	Referent	956	1.00	Referent	4,304	1.00	Referent
0.01–0.24	2,693	1.09	0.89, 1.34	716	1.18	0.89, 1.58	3,409	1.11	0.94, 1.32
0.25–1.00	1,864	1.44	1.13, 1.85	569	1.26	0.90, 1.77	2,433	1.42	1.14, 1.77
Continuous	7,905	2.29	1.38, 3.81	2,241	1.52	0.74, 3.13	10,146	2.17	1.41, 3.34
Calculus index									
Categorical									
0–0.24	2,597	1.00	Referent	584	1.00	Referent	3,181	1.00	Referent
0.25–0.74	2,732	1.02	0.81, 1.29	715	1.03	0.76, 1.38	3,447	1.04	0.86, 1.24
0.75–2.00	2,576	1.39	1.03, 1.87	942	1.36	0.90, 2.05	3,518	1.39	1.08, 1.79
Continuous	7,905	1.48	1.13, 1.93	2,241	1.28	0.93, 1.76	10,146	1.42	1.12, 1.80
Periodontal disease (PD) status§									
Categorical									
Non-PD	1,415	1.00	Referent	272	1.00	Referent	1,687	1.00	Referent
Mild PD	4,238	0.81	0.65, 1.50	925	0.87	0.57, 1.32	5,163	0.83	0.67, 1.02
PD	2,252	1.13	0.85, 1.50	1,044	1.12	0.73, 1.71	3,296	1.15	0.91, 1.45
Continuous	7,905	1.08	0.96, 1.23	2,241	1.14	0.94, 1.39	10,146	1.12	1.00, 1.25

* $p < 0.05$; ** $p < 0.01$.

† OR, odds ratio; 95% CI, 95% confidence interval.

‡ SUDAAN software and weights provided in NHANES III data were used, and age, ethnicity, education, sex, family size, poverty index, body mass index, family history of heart attack, diabetes status, smoking, chewing tobacco, and alcohol use were adjusted for using multiple logistic regression.

§ Non-PD, no tooth with pocket depth ≥2 mm or attachment loss ≥3 mm; mild PD, at least one tooth with pocket depth ≥2 mm or attachment loss ≥3 mm; PD, at least one tooth with pocket depth ≥3 mm or attachment loss ≥4 mm.

and coagulation complications associated with atherosclerosis (32, 33). Monocyte-derived cytokines, such as tumor necrosis factor and interleukins 1, 6, and 8, have powerful effects on hepatic protein synthesis (e.g., in upregulating fibrinogen synthesis), tissue catabolism, and lipid metabolism (34). Both tumor necrosis factor and interlelukin-1 inhibit the production of lipoprotein lipase, causing lipid metabolism disturbance (35).

The commonly observed lipid abnormalities related to infection in humans and experimental animals, although not necessarily applying to human periodontal infection, include increased very low density lipoprotein levels (36–38) as well as decreased HDL cholesterol level (15, 39, 40). Infections other than periodontal disease have been found to be associated with increased blood viscosity by raising plasma fibrinogen and other factors (41–43). One study also reported elevated circulating fibrinogen among individuals with periodontitis (11). A recent study (44) has found that, compared with people with neither periodontitis nor cardiovascular disease, the C-reactive protein level was doubled in those with only one of the diseases and five times higher for those with both diseases.

The effect of poor periodontal health status on these well-established CVD risk factors may explain, at least in part, the association between periodontal disease and increased CVD risk observed in a number of previous studies (4–12). Serum cholesterol and plasma fibrinogen are well-established CVD risk factors (45–54). It is estimated that a 1 percent increase in the serum total cholesterol level will result in about a 2 percent increase in the risk for CHD (48, 49). Fibrinogen can promote early plaque formation through damaging the endothelial cells of artery linings, stimulating the proliferation of vascular muscle cells, and activating inflammatory cells (51, 52). Fibrinogen also plays an important role in thrombosis by influencing platelet adhesion and aggregation (52). C-reactive protein, a marker for underlying systemic inflammation, has also been found to be an independent risk factor for both recurrent ischemia among patients with unstable angina (53) and incident myocardial infarction and ischemic stroke among healthy men (54). Thus, it is possible that these CVD risk factors may serve as intermediate variables linking periodontal disease to elevated CVD risk.

TABLE 6. Differences in means and regression coefficients for plasma fibrinogen (mg/dl) by periodontal health status, Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994

	Age 17–54			Age ≥55			Total		
	Sample size (no.)	Mean†	Difference/ β‡	Sample size (no.)	Mean†	Difference/ β	Sample size (no.)	Mean†	Difference/ β
Gingival bleeding index									
Categorical									
0	993	288.38	0.00 (referent)	950	314.30	0.00 (referent)	1,943	298.13	0.00 (referent)
0.01–0.24	731		1.80 (4.92)§	716		0.64 (6.11)	1,447		1.74 (4.39)
0.25–1.00	504		−7.03 (7.49)	567		6.12 (7.68)	1,071		−0.82 (6.10)
Continuous	2,228		−4.11 (14.97)	2,233		8.16 (7.68)	4,461		2.17 (11.64)
Calculus index									
Categorical									
0–0.24	635	279.68	0.00 (referent)	576	312.63	0.00 (referent)	1,211	292.12	0.00 (referent)
0.25–0.74	748		5.41 (5.94)	710		1.00 (4.78)	1,458		3.75 (4.10)
0.75–2.00	845		20.39 (8.02)*	947		7.09 (7.94)	1,792		14.97 (6.76)*
Continuous	2,228		14.04 (4.68)**	2,233		8.40 (6.14)	4,461		11.89 (4.18)**
Periodontal disease (PD) status¶									
Categorical									
Non-PD	348	287.09	0.00 (referent)	272	313.39	0.00 (referent)	620	296.78	0.00 (referent)
Mild PD	1,087		−2.08 (4.63)	922		−3.20 (9.49)	2,009		−2.75 (5.07)
PD	793		7.27 (7.25)	1,039		8.00 (7.87)	1,832		8.19 (5.31)
Continuous	2,228		4.21 (3.11)	2,233		4.34 (3.03)	4,461		4.52 (2.13)*

* $p < 0.05$; ** $p < 0.01$.

† SUDAAN software and weights provided in NHANES III data were used, and age, ethnicity, education, sex, family size, poverty index, body mass index, family history of heart attack, diabetes status, smoking, chewing tobacco, and alcohol use were adjusted for using multiple linear regression. Mean fibrinogen was calculated from the regressions using mean values of all covariates.

‡ β, regression coefficient for the continuous variable of periodontal health status; referent, referent group in comparison of differences in means.

§ Numbers in parentheses, standard error.

¶ Non-PD, no tooth with pocket depth ≥2 mm or attachment loss ≥3 mm; mild PD, at least one tooth with pocket depth ≥2 mm or attachment loss ≥3 mm; PD, at least one tooth with pocket depth ≥3 mm or attachment loss ≥4 mm.

This study has several strengths. First, it used data from NHANES III, which represents the US national population. Therefore, findings from this study have good external validity in comparison with other studies in which study samples were restricted to local populations. Second, statistical analyses were performed with adjustment for a number of potential confounders. Covariates such as age, sex, educational attainment, income level, cigarette smoking, alcohol use, diabetes status, and body mass index were included. Third, application of weights and adjustment for the NHANES III design feature are considered in our analyses. Theoretically, routine analyses based on the assumption of a simple random sample are not applicable, because of the complex survey design used in NHANES III (23). Therefore, our analyses are likely to generate unbiased national estimates.

Gingival bleeding, the calculus index, and periodontal disease status defined by the severity of periodontal pocket depth and periodontal attachment loss were used to measure periodontal health. While these indicators are highly correlated, they may reflect somewhat different aspects of periodontal health. The gingival bleeding index, for example, may indicate an acute gingival inflammation level, while periodontal disease status indicates long-term destruction of the periodontal tissue. Dental calculus, the calcified dental plaque, plays a role in maintaining and promoting the formation of plaque that consists of a dense mass of microorganisms (55, 56). This study was able to examine the association between each of the indicators for periodontal health and CVD risk factors of interest, providing more detailed analyses. For example, elevated C-reactive protein tended to be more closely related to poor gingival bleeding than poor periodontal disease status.

It also needs to be kept in mind that this study may be subject to several limitations. First, indicators for both acute periodontal inflammation and chronic periodontal destruction were used to measure periodontal status. These indicators did not directly measure the causal microorganisms per se. Thus, even though an association between poor periodontal status and elevated risk factors for CVD was observed, further stud-

TABLE 7. Multiple logistic regressions for serum C-reactive protein (n = 10,141) and multiple linear regressions for plasma fibrinogen (n = 4,461), Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994

	C-reactive protein† (β coefficient)‡	Fibrinogen (β coefficient)
Intercept	−5.95 (0.66)**,§	154.33 (34.66)**
Calculus index¶	0.35 (0.12)**	11.89 (4.18)**
Ethnicity (referent = other)		
White	−0.29 (0.19)	1.78 (8.06)
Black	0.07 (0.18)	6.96 (7.67)
Mexican	−0.13 (0.19)	−2.10 (9.17)
Years of schooling	−0.04 (0.02)*	−0.87 (0.64)
Sex (female vs. male)	1.04 (0.11)**	14.52 (2.85)**
Age in years	0.02 (0.01)**	1.12 (0.20)**
Family size (no.)	−0.01 (0.02)	−0.91 (1.04)
Poverty index	−0.03 (0.03)	0.71 (1.05)
Body mass index (kg/m^2)	0.13 (0.01)**	2.34 (0.33)**
Family history of myocardial infarction (yes vs. no)	0.09 (0.15)	−1.52 (5.38)
Diabetes (yes vs. no)	−0.23 (0.18)	−6.48 (9.12)
Chewing tobacco (yes vs. no)	0.08 (0.17)	−4.77 (8.60)
Drinks per day (no.)	−0.04 (0.05)	−4.93 (1.41)**
Cigarettes per day (no.)	0.02 (0.01)**	0 89 (0.21)**
Exsmoker (yes vs. no)	0.17 (0.08)*	2.31 (2.92)

* $p < 0.05$; ** $p < 0$ 01.
† C-reactive protein was categorized into two levels: ≥0.4 mg/dl and <0.4 mg/dl.
‡ β, regression coefficient. Regression analyses were performed with weighting using SUDAAN statistical software.
§ Numbers in parentheses, standard error.
¶ Calculus index was analyzed as continuous variables.

ies are needed to confirm the possible role of specific harmful microorganisms in the observed association.

The observed associations between periodontal status and CVD risk factors generally support the existence of possible pathways that link periodontal disease to CVD. However, since cross-sectional data were used, the temporal sequence between periodontal status and CVD risk factors studied cannot be explicitly established. For example, a hypersensitive inflammatory trait could predispose to periodontal disease and elevated C-reactive protein and fibrinogen. Thus, a spurious association between periodontal status and these CVD risk factors is not impossible. In addition, since a low fibrinogen concentration may elicit a high tendency toward gingival bleeding, gingival bleeding assessment may not be a good indicator for periodontal health in the examination of the effect of periodontal infection on the plasma fibrinogen concentration. This may at least partially explain why no consistent association was observed between the gingival bleeding index and the fibrinogen concentration in comparison with the association observed between the other periodontal measurements and the fibrinogen concentration.

Probing was used as a basic technique to measure periodontal status (gingival bleeding and periodontal pocket and attachment loss) in this study. Measurement error in probing is related to several factors including probing force and gingival condition (57). In this study, a highly standardized protocol was used to minimize measurement error. In addition, a number of periodontal sites were measured, and study subjects were restricted to those who had at least six teeth examined. The restriction to six or more teeth would improve the reliability of the periodontal measurements, but the teeth with worse disease may be extracted; hence, the remaining teeth may not represent the long-term periodontal status. As missing teeth were not taken into account in the measurements for periodontal status, the association between periodontal health and CVD factors may be underestimated, especially in the analyses for participants aged 55 years and older. This age group tends to have more missing teeth. This may explain at least in part the somewhat weaker relation of periodontal status with C-reactive protein and fibrinogen in this age group than in those aged 17–54 years.

It also is noteworthy that there may be other potential pathways underlying the association between periodontal disease and increased CVD risk. Bacteria, lipopolysaccharide, and other bacterial products associated with periodontal disease have been hypothesized to directly attack the arterial lining, damage the endothelial cells, aggregate platelets, and cause subsequent clinical CVD events. Therefore, more studies are needed to clarify the role of periodontal disease in the etiology and development of CVD.

In summary, this study suggests that poor periodontal health status is associated with elevated serum total cholesterol, C-reactive protein, and plasma fibrinogen, which may explain, at least in part, the link between periodontal disease and increased CVD risk.

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