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Serum antibodies to periodontal pathogens and markers of systemic inflammation

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Abstract

Aim: We examined the relationship between serum antibodies against *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans*, and plasma fibrinogen and serum C-reactive protein (CRP) in a nationally representative sample.

Methods: Data on 2973 participants aged 40 years and older from the third National Health and Nutrition Examination Survey, second phase (1991–1994) were used. Three logistic regression models adjusted for gender, race, educational attainment, diabetes, cigarette smoking, body mass index (BMI), and other inflammatory conditions were constructed, based on three different assumptions: (A) no access to dental/periodontal data; (B) knowledge of number of teeth present but not of clinical periodontal status; and (C) knowledge of both dental and clinical periodontal status.

Results: High fibrinogen (>400 mg/dl) was unrelated to *P. gingivalis* and *A. actinomycetemcomitans* antibodies in all models. High CRP (>0.4 mg/dl) was related to high antibody levels to *P. gingivalis* in models A [odds ratios (OR) 1.63, 95% confidence intervals (CI) 1.15–2.32], B (OR 1.69, 95% CI 1.18–2.41), and C (OR 1.58, 95% CI 1.12–2.23). In model C, high CRP was related to $>30\%$ extent of attachment loss of $\geqslant 3$ mm (OR 1.58, 95% CI 1.19–2.08). Antibodies to *A. actinomycetemcomitans* were not associated with high CRP levels in any model.

Conclusions: High serum titre to *P. gingivalis* and the presence of periodontal disease are independently related to high CRP levels.

Key words: *Actinobacillus actinomycetemcomitans*; antibody; C-reactive protein; fibrinogen; IgG; NHANES III; periodontitis; *Porphyromonas gingivalis*

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Chronic bacterial and viral infections have been hypothesized to promote atherogenesis and increase the associated risk for cardiovascular disease (CVD), (Epstein et al. 1999). Over the last decade, mounting evidence from epidemiologic studies suggests that periodontitis, a bacterial infection of the periodontal tissues and a leading cause of tooth loss in the elderly, may be an independent risk factor for atherosclerosis and CVD (Mattila et al. 1993, Beck et al. 1996, Beck et al. 2001). Multiple pathways supporting the biological plausibility of the proposed effect have been described and explored. These include occurrence of transient bacteremias, elevation of inflammatory mediators in the systemic circulation in response to bacterial factors, endothelial and smooth muscle cell activation, and molecular mimicry between bacterial and self- antigens (for review see (Genco et al. 2002)). Alternatively, this association has been proposed to reflect the effect of common risk factors for periodontitis and CVD, with the findings likely being a product of residual confounding because of inadequate adjustment for smoking (Hujoel et al. 2000, Hujoel et al. 2003).

A major criticism of the literature that deals with the association between periodontitis and CVD is the fact that most studies have only employed clinical markers of periodontal disease as measures of exposure, rather than variables directly linked to infection (Beck & Offenbacher 2005). Such candidate markers could include the quantification of specific subgingival microbiota as well as the assessment of systemic antibody responses to the oral microbial challenge, to determine both the intensity and the quality of the infectious burden.

With few exceptions, the role of serum antibodies to periodontal bacteria has not been adequately explored in the context of a periodontitis-mediated risk for CVD. These responses merit further study as they may provide an alternative assessment of periodontal status instead of the traditional clinical examination. Whereas serum samples that allow the study of systemic antibody responses to infectious agents are routinely collected

in most major epidemiologic studies, data on periodontal microbiota or clinical markers of periodontitis are relatively sparse. Previous work has demonstrated that patients with periodontitis generally have higher titres against specific periodontal bacteria than individuals with low levels of disease (Naito et al. 1984, Kinane et al. 1999, Papapanou et al. 2001, Papapanou et al. 2004). Therefore, an association between serological markers of periodontitis and inflammatory factors that have been linked mechanistically to the atherosclerotic process could be potentially of value in ascribing the proportion of the total infection-mediated risk for CVD that can be attributed to periodontitis.

In this study, we used data from a nationally representative sample of dentate subjects from whom clinical periodontal information was available to examine the relationship between serum IgG responses to two major periodontal pathogens, *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans*, and two important inflammatory proteins [C-reactive protein (CRP) and fibrinogen] that have been shown in epidemiologic studies to be predictors of atherosclerosis, cardiovascular, and ischaemic events (Sweetnam et al. 1996, Folsom et al. 1997, Cushman et al. 1999, Koenig et al. 1999, Ridker et al. 2000, Smith et al. 2000, Ridker et al. 2001, Bickel et al. 2002, Koenig et al. 2004, Rutter et al. 2004).

Methods

Study population

We used data from 2973 adults who participated in the second phase of the third National Health and Nutrition Examination Survey (NHANES III, 1991–94). The NHANES III survey was comprised of two 3-year phases (1988–91 and 1991–94) and was conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. A complex, stratified, multistage probability design was used to produce a nationally representative sample of the non-institutionalized civilian population of the United States for each phase of NHANES III. Individuals who were either less than 6 years of age or older than 60 years, Mexican American, or non-Hispanic black were oversampled in NHANES III. Details of the sample design and methods used to obtain informed consent from study participants have been described elsewhere (NHANES III 1992, 1994).

Sociodemographic information and smoking history were collected during an interview in the home of the participant. A standardized oral health examination and venipuncture were performed at a mobile examination center (MEC). All dental examinations were performed by trained dentists who were periodically calibrated by the survey's expert dental examiner. Examiner consistency and reliability during the periodontal assessment were considered to be good (Winn et al. 1999). During phase 2, the majority of dental examinations was performed by two dentists. Detailed information about the NHANES III oral health assessment protocols, quality control, and measurement issues have been described elsewhere (Drury et al. 1996).

Serum CRP concentration was determined by a nephelometric immunoassay with a lower detection limit of 0.3 mg/dl. Serum cholesterol was analysed enzymatically using a commercially available reagent mixture, and high-density lipoprotein (HDL) cholesterol was measured after precipitating other lipoproteins using a heparin-manganese chloride process. Plasma fibrinogen levels were measured by comparing clotting time with a standardized fibrinogen preparation using a Coag-A-Mate XC Plus analyser (Organon Teknika, Durham, NC, USA). Only sampled persons aged 40 years or older received a fibrinogen assessment. Laboratory procedures, analytical methods, and quality control have been described elsewhere (NHANES III 1996).

Sera were analysed for IgG antibodies to *A. actinomycetemcomitans* and *P. gingivalis* using only phase 2 (1991–94) blood from the NHANES III surplus sera collection. These analyses were carried out in samples from persons aged 12 years or older using an enzyme-linked immunoassay (ELISA) for IgG antibodies against *A. actinomycetemcomitans* and *P. gingivalis*. Testing was performed by a National Institute of Dental and Craniofacial Research (NIDCR) lab contractor. Additional background information regarding the NHANES III *A. actinomycetemcomitans* and *P. gingivalis* titre levels have been published elsewhere (NHA NES III 2001).

For our study, we used data from four NHANES III data files (http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm). Data were obtained from questionnaire information (the Adult File), a standardized oral health examination (the Exam File), sera and plasma assessments (the Lab File), and *A. actinomycetemcomitans* and *P. gingivalis* surplus sera assessments (the Periodontal Pathogen Antibody File). We identified a total of 9930 adults who had an interview recorded in the NHANES III phase 2 Adult File. We excluded 4379 persons who were under the age of 40 years and 747 participants who did not receive an MEC examination. We then excluded 1047 persons who were edentulous and 297 persons who did not have complete lab information for CRP, fibrinogen, and *A. actinomycetemcomitans* or *P. gingivalis* antibodies. Next, we excluded 349 individuals who did not have a complete periodontal examination. From this remaining group, we excluded 138 persons with *A. actinomycetemcomitans* and *P. gingivalis* antibody titres either among the upper or lower 1% of reported values to minimize the effects of extreme values. This yielded an analytical sample of 2973 participants used for all subsequent analyses.

Outcome variables

CRP and fibrinogen were the two dependent variables used in our analysis. Although we present mean values with standard errors for both variables, all statistical analyses were performed using dichotomized values for these variables. If a person had a CRP value >0.40 mg/dl, he or she was classified as having a ''high'' CRP blood level. The rationale for this a priori determined cut-off has been previously discussed (Wu et al. 2000a). We defined individuals as having ''high'' fibrinogen blood levels when fibrinogen concentrations were >400 mg/dl. Findings from prospective studies have indicated that patients with mean fibrinogen levels ranging from 320 to 400 mg/dl are more likely to experience recurrent acute coronary and stroke events, and that this likelihood increases linearly with high fibrinogen levels (Thompson et al. 1995, Rothwell et al. 2004). In the Framingham study, healthy participants were more likely to experience cardiovascular events if antecedent fibrinogen levels were greater than 310 mg/dl (Kannel et al. 1987).

Covariate selection

Individuals were categorized into three age groups: those 40–54, 55–69 years-old, and those aged 70 years or older. Race/ethnicity was categorized as Mexican-American, non-Hispanic black, and non-Hispanic white. Adults who were identified as ''other'' were included in the total population estimates, but not in the regression analyses. Poverty status was dichotomized as either equal to or below 130% of the federal poverty level or greater than 130%. This was calculated by dividing total family income by the adjusted federal poverty income threshold. We categorized educational attainment as ''not completing high school,'' ''completing high school,'' and having ''at least some college experience.'' Other demographic variables included in our analyses were region (northeast, midwest, south, and west) and sex.

Cigarette smoking status was categorized as either current smoker, former smoker, or never smoked. Individuals who reported that they had smoked at least 100 cigarettes (approximately five packs) in their lifetime but no longer smoked cigarettes were classified as former smokers. Individuals reporting a prior diagnosis of diabetes by a physician were classified as a diagnosed diabetic. Following previously reported guidelines, women who appeared to have only gestational diabetes were categorized as not having diagnosed diabetes (Harris et al. 1998). We created a total cholesterol-HDL (TC-HDL) ratio based upon a proposed model developed for assessing cardiovascular risk (Rifai & Ridker 2001). Persons with a value in the upper fifth-quintile were defined as having a ''high'' TC-HDL value. Individuals were determined to have ''other potential inflammatory conditions'' if they had either creatinine levels indicating renal dysfunction (serum levels >3.0 mg/dl), reported having rheumatoid or osteoarthritis, or reported taking oral oestrogen. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres. Pregnant females were excluded from the BMI calculation. We used federal guidelines to categorize BMI levels as follows: a BMI of 30 or greater (obese), a BMI of 25 to less than 30 (overweight), and a BMI less than 25 (not overweight or obese) (NHLBI Panel, 1999).

We determined ''elevated'' *A. actinomycetemcomitans* and *P. gingivalis* antibody titres by selecting a titre level at 90% or higher in those without periodontal disease after excluding individuals in the upper most and lowest one percent of the *A. actinomycetemcomitans* and *P. gingivalis* lab value range. This yielded cut points of 156 and 168 equivalent units (U) for *A. actinomycetemcomitans* and *P. gingivalis*, respectively. Consequently, persons were defined as having an elevated antibody titre for *A. actinomycetemcomitans* and *P. gingivalis* when concentrations were $\geqslant$ 156 and 168 U, respectively. Persons who had at least one periodontal site with 3 mm or more loss of attachment (LOA) and 4 mm or more of pocket depth (PD) were categorized as having periodontal disease. These criteria have been previously reported (Arbes et al. 2001).

We quantified the extent and severity of periodontitis by using a combination of attachment loss and PD measurements. Thus, periodontitis was considered present if a subject had at least one site with 3 mm or more of LOA and a concomitant PD of 4 mm or more. We next calculated an extent figure for each subject by summing up all sites with 3 mm or more LOA and a concomitant PD of 4 mm or more and dividing it by the number of dental sites evaluated, and further categorized it as ''high'' if $\geqslant$15% and ''low'' if $<15\%$. Gingival bleeding extent was categorized as 0–18% and 19% or more of the sites showing bleeding. Dentate status was characterized as having less than 10 teeth, having 10–19 teeth, or having more than 19 teeth present.

Data analysis

All statistical analyses were performed using SUDAAN software (version 7.5, RTI, Research Triangle Park, NC, USA). We used examination sample weights to account for the unequal probability of selection and non-response of the study participants to produce estimates, relative odds, and related standard errors. We used pairwise *t*-tests to assess for significant differences ($p<0.05$) between groups. We used logistic regression models to compute adjusted odds ratios (OR) and 95% confidence intervals (CI). Potential two-way interactions were explored throughout the modelling process. A $p<0.05$ was considered statistically significant.

Modelling was performed under three considerations for each of the two dependent variables examined. The first approach (A) was to produce models under the assumption that no dental clinical measures were available, but serology measures were available. The second approach (B) was to produce models under the assumption that no clinical periodontal measures were available, but serology and basic dentate status information were available. The third approach (C) was to produce models using all available dental clinical measures and serology. We used non-automated stepwise regression modelling to assess the relationships between the hypothesized explanatory variables and the outcome variables for each of the three approaches. We started with a simple model and began sequentially adding relevant covariates to produce a ''full model'' for each approach. Parsimonious models were determined by covariate exclusion from the ''full models'' with criteria for inclusion set for a Satterthwaite-adjusted *F* statistic with a $p<0.05$.

Results

Among the non-institutionalized, dentate population of the US aged 40 years or older, 10% have elevated titre levels to *A. actinomycetemcomitans* and 10.8% have elevated titre levels to *P. gingivalis* (Table 1). Mexican Americans, non-Hispanic blacks, persons not completing

Table 1. The sample size, weighted percent, and standard errors (SE) for adults aged 40 years or older with elevated titre to *A. actinomycetemcomitans* (Aa) and *P. gingivalis* (Pg) by selected characteristics: United States 1991–94[†]

Characteristic	Sample size	Aa elevated[‡] % (SE)	Pg elevated[§] % (SE)
Total	2973	10.0(1.3)	10.8 (0.9)
Age			
70+years	655	9.6 (1.9)	12.4 (2.5)
55–69 years	946	11.6 (2.0)	11.9 (1.2)
40–54 years[¶]	1372	9.3 (1.7)	9.8 (1.3)
Sex			
Men	1355	10.7 (1.6)	11.1 (1.0)
Women[¶]	1616	9.4 (1.5)	10.6 (1.2)

Table 1. (Contd.)

Characteristic	Sample size	Aa elevated[‡] % (SE)	Pg elevated[§] % (SE)
Race/ethnicity			
Mexican American	771	15.4 (1.0)*	19.8 (2.1)*
Non-Hispanic black	759	13.1 (1.4)*	25.3 (1.7)*
Non-Hispanic white[¶]	1302	8.1 (1.5)	7.7 (1.1)
Education attainment			
Not completed High school	1189	16.1 (2.3)*	15.8 (1.7)*
Completed high school	911	7.9 (1.5)	11.1 (1.6)
Some college[¶]	850	8.4 (1.9)	8.0 (1.3)
Poverty			
⩽130% fed poverty line	779	10.8 (1.4)	21.6 (3.1)*
>130% federal poverty line[¶]	1939	9.3 (1.6)	9.4 (0.8)
Cigarette smoking			
Current smoker	628	5.6 (2.2)	8.2 (1.4)*
Former smoker	874	11.9 (1.8)	9.3 (1.5)
Never smoked[¶]	1471	10.5 (1.5)	13.0 (1.2)
Region			
Northeast	471	15.3 (3.2)*	9.3 (1.9)
Midwest	541	11.4 (3.9)	9.0(2.5)
South	1421	8.1 (1.0)	12.4 (1.7)
West[¶]	540	6.0 (1.0)	12.0 (1.4)
Other potential inflammatory conditions[‖]			
Yes	684	5.2 (1.0)*	8.8 (1.1)*
No[¶]	2289	11.5 (1.5)	11.4 (1.0)
Diagnosed diabetic			
Yes	314	8.3 (2.1)	14.4 (2.4)
No[¶]	2659	10.1 (1.4)	10.5 (0.9)
TC-HDL ratio[**]			
High	514	9.2 (2.2)	9.3 (1.8)
Lower[¶]	2417	10.2 (1.4)	11.2 (0.9)
BMI Level			
⩾30	953	10.9 (1.8)	11.4 (1.7)
25 to<30	1142	9.6 (1.5)	11.4 (0.9)
<25[¶]	873	9.6 (2.0)	9.7 (1.4)
Dentate status			
1–9 Teeth	348	7.0 (2.8)	11.9 (2.4)
10–19 Teeth	680	12.1 (1.9)	12.3 (1.6)
20+Teeth[¶]	1945	9.9 (1.6)	10.3 (1.1)
Gingival bleeding			
19–100% extent	642	16.5 (2.0)*	21.1 (2.6)*
0–18% extent[¶]	2331	8.8 (1.3)	8.9 (0.9)
Attachment loss 3 mm			
46–100% extent	544	10.9 (2.3)	20.3 (2.7)*
31–45% extent	258	13.0 (3.6)	15.5 (4.0)
16–30% extent	453	18.6 (4.1)*	14.3 (1.9)*
0–15% extent[¶]	1718	7.7 (1.1)	7.7 (0.8)
Periodontal disease present[††]			
Yes	588	16.1 (3.4)*	24.3 (3.2)*
No[¶]	2385	9.8 (1.3)	9.7 (0.6)
Periodontal disease extent[‡‡]			
High	152	11.1 (3.1)	36.2 (6.8)*
Lower[¶]	2821	9.9 (1.4)	10.0 (0.8)

*$p<0.05$ compared with the reference category (pairwise comparison for dichotomous CRP and Fibrinogen only).

[†]NHANES III phase 2 sample only.

[‡]Elevated Aa: titre level ⩾156 U.

[§]Elevated Pg: titre level ⩾168 U.

[¶]Reference category.

[‖]Other potential inflammatory conditions: creatinine levels indicate renal failure, reports taking oral estrogen, or reports having osteo/rheumatoid arthritis.

[††]Periodontal disease defined as having at least 1 site with LOA ⩾ 3 mm and PD ⩾ 4 mm.

[‡‡]Periodontal disease extent defined as having LOA ⩾ 3 mm and PD ⩾ 4 mm at the same site in 15% or more of the sites.

[**]Total cholesterol-HDL ratio – high value: in the upper fifth-quintile.

HDL, total cholesterol-high-density lipoprotein; BMI, body mass index; NHANES III, third National Health and Nutrition Examination Survey; LOA, loss of attachment; PD, pocket depth.

high school, or those residing in the Northeast are more likely to have elevated *A. actinomycetemcomitans* titre compared with non-Hispanic whites, persons with higher levels of educational attainment, or those living in the West, respectively. A higher percent of individuals with periodontal disease present have high *A. actinomycetemcomitans* titres compared with those without periodontal disease (16.1% and 9.8%, respectively). The percent with elevated *P. gingivalis* is higher among non-Hispanic blacks (25.3%) compared with non-Hispanic whites (7.7%) and among those living at or below 130% of the federal poverty line (21.6%) compared with those living above 130% of the federal poverty line (9.4%). A higher percent of individuals with prevalent periodontal disease or greater disease extent have elevated *P. gingivalis* titres (24.3% and 36.2%, respectively) compared with those without periodontal disease (8.7% and 10.0%, respectively).

The weighted mean and percent with high blood levels for fibrinogen and CRP are shown in Table 2. In the US, non-Hispanic blacks are more likely to have high fibrinogen and CRP levels compared with non-Hispanic whites (12.7% and 34.6% versus 6.8% and 22.4%, respectively). Women, persons with lower educational attainment, those living in poverty, or having a diagnosis of diabetes are more likely to have high fibrinogen and CRP levels compared with men, persons with some college experience, those not living in poverty, or those not diagnosed with diabetes. Obese and overweight individuals are more likely to have high CRP levels compared with those who are not overweight or obese. Persons with less than 20 teeth, having elevated *P. gingivalis* antibody titre, and experiencing more than 30% attachment loss at 3 mm are more likely to have high CRP levels compared with those with 20 or more teeth, lower *P. gingivalis* titre, and attachment loss affecting 30% of the dentition or less. Persons with prevalent periodontal disease are more likely to have high fibrinogen levels compared with those without the disease (11.6% versus 7.0%).

The logistic regression results for high fibrinogen are presented in Table 3. In a multivariate model (Model 1) with no clinical dental measures (Approach A), high fibrinogen is significantly associated ($p<0.05$) with female gender and lower educational attainment. These relationships remain unchanged if information pertaining to basic dentate

status (Approach B) or periodontal measures (Approach C) are included in the analysis (Model 1). In a parsimonious multivariate model (Model 2) with no clinical dental measures (Approach A), high fibrinogen is significantly associated with female gender, not completing high school, and being diagnosed with diabetes. However, when periodontal measures (Approach C) are included in the modelling, persons with prevalent periodontal disease are more likely to have high fibrinogen (OR = 1.64, 95% CI = 1.10, 2.44) compared with those without the disease (Model 2). Gender, educational attainment, and diabetic status remain unchanged. Elevated *A. actinomycetemcomitans* and *P. gingivalis* titres are not associated with high fibrinogen in these multivariate models.

Table 4 shows the regression results for high CRP. In a multivariate model (Model 1) with no clinical dental measures (Approach A), high CRP is significantly associated ($p < 0.05$) with female gender, current cigarette smoking, having other potential inflammatory conditions, and having a BMI of 25 or greater. Individuals with an elevated *P. gingivalis* antibody titre also are more likely to have high CRP levels compared with those with a lower *P. gingivalis* titre (OR = 1.69, 95% CI = 1.18, 2.42) in this multivariate model. These relationships remain unchanged if information pertaining to basic dentate status (Approach B) or periodontal measures (Approach C) are included in the analysis (Model 1).

In a parsimonious multivariate model (Model 2) with no clinical dental measures (Approach A), high CRP is significantly associated with female gender, lower educational attainment, having other potential inflammatory conditions, and having higher BMI levels. Individuals with an elevated *P. gingivalis* antibody titre also are more likely to have high CRP levels compared with those with a lower *P. gingivalis* titre (OR = 1.63, 95% CI = 1.15, 2.32) in this parsimonious model.

In a parsimonious model (Model 2) incorporating basic dentate status (Approach B), individuals with nine teeth or less are more likely to have high CRP levels compared with those with 20 or more teeth (OR = 1.39, 95% CI = 1.09, 1.86). High CRP also is associated with female gender, being non-Hispanic black, having other potential inflammatory conditions, being obese or overweight, and elevated *P. gingivalis* antibody titres. When periodontal measures (Approach C) are included in the modelling (Model 2), persons with LOA greater than 30% are more likely to have high CRP levels compared with those with attachment loss affecting 30% of the dentition or less (OR = 1.58, 95% CI = 1.19, 2.08). The odds of having high CRP for

Table 2. The weighted mean, percentage of high blood levels, and related standard errors (SE) for fibrinogen and CRP by selected characteristics for adults aged 40 years or older: United States 1991–94[†]

Characteristic	Fibrinogen[‡] mean (SE)	High fibrinogen[§] (SE) %	CRP[‡] mean (SE)	High CRP[§] % (SE)
Total	300.1 (3.0)	7.6 (0.9)	0.44 (0.01)	23.7 (1.6)
Age				
70+years	321.9 (4.2)	11.1 (1.8)*	0.50 (0.03)	26.5 (2.1)
55–69 years	306.9 (4.5)	9.4 (1.6)*	0.49 (0.03)	26.4 (2.6)
40–54 years[¶]	290.9 (4.0)	5.9 (1.3)	0.40 (0.02)	21.5 (2.2)
Sex				
Women	308.4 (3.1)	9.1 (1.1)*	0.51 (0.02)	29.4 (2.4)*
Men[¶]	291.1 (4.0)	6.1 (1.0)	0.37 (0.02)	17.4 (1.6)
Race/ethnicity				
Mexican american	301.6 (2.7)	6.9 (0.8)	0.50 (0.02)	27.1 (1.4)*
Non-hispanic black	311.5 (2.5)	12.7 (1.6)*	0.59 (0.03)	34.6 (1.8)*
Non-Hispanic white[¶]	298.8 (3.4)	6.8 (1.2)	0.42 (0.02)	22.4 (1.9)
Education attainment				
Not completed high school	318.3 (5.9)	11.4 (2.3)*	0.49 (0.02)	29.7 (1.9)*
Completed high school	301.5 (3.6)	8.0 (1.0)*	0.46 (0.04)	27.4 (2.8)*
Some college[¶]	290.3 (2.5)	5.5 (1.0)	0.40 (0.03)	18.0 (1.7)
Poverty				
⩽130% Fed poverty line	322.4 (8.2)	11.8 (2.1)*	0.65 (0.06)	34.1 (2.9)*
>130% Federal poverty line[¶]	296.1 (3.4)	6.7 (1.1)	0.41 (0.01)	22.3 (1.8)
Cigarette smoking				
Current smoker	309.1 (4.5)	7.9 (1.4)	0.50 (0.04)	27.4 (3.4)
Former smoker	300.1 (4.2)	8.4 (1.0)	0.44 (0.03)	22.9 (2.4)
Never smoked[¶]	296.4 (3.9)	7.0 (1.4)	0.41 (0.02)	22.2 (1.6)
Region				
Northeast	309.7 (5.2)	9.4 (1.4)*	0.40 (0.03)	23.9 (4.6)
Midwest	295.3 (9.2)	7.2 (3.0)	0.46 (0.03)	24.1 (2.5)
South	302.6 (3.9	8.5 (1.4)	0.47 (0.02)	26.1 (1.8)*
West[¶]	291.7 (6.2)	5.0 (1.3)	0.41 (0.03)	19.1 (2.8)
Other potential inflammatory conditions[‖]				
Yes	304.7 (3.8)	8.5 (1.2)	0.50 (0.03)	31.8 (2.1)*
No[¶]	298.7 (3.3)	7.4 (1.1)	0.42 (0.02)	21.1 (1.8)
Diagnosed diabetic				
Yes	324.5 (9.9)	12.3 (2.1)*	0.74 (0.07)	36.2 (5.9)*
No[¶]	298.4 (3.0)	7.3 (0.9)	0.42 (0.01)	22.8 (1.8)
BMI Level				
⩾30	310.9 (5.0)	9.7 (1.8)	0.55 (0.03)	36.0 (2.9)*
25 to<30	296.9 (3.9)	6.2 (1.3)	0.40 (0.01)	23.0 (2.1)*
<25[¶]	294.1 (4.7)	7.4 (1.3)	0.38 (0.02)	13.4 (1.2)
TC-HDL ratio**				
High	302.4 (5.1)	7.8 (1.8)	0.46 (0.04)	23.8 (2.5)
Lower[¶]	300.3 (3.0)	7.7 (1.0)	0.43 (0.01)	23.5 (1.8)
Aa Elevated titre[††]				
Yes	310.9 (13.)	10.7 (4.6)	0.47 (0.04)	31.3 (6.2)
No[¶]	298.9 (2.5)	7.3 (0.8)	0.44 (0.01)	22.8 (1.3)
Pg Elevated titre[‡‡]				
Yes	306.9 (6.2)	7.5 (1.7)	0.54 (0.04)	31.3 (3.2)*
No[¶]	299.3 (3.2)	7.7 (1.0)	0.43 (0.01)	22.7 (1.7)
Dentate status				
<10 teeth	313.4 (5.5)	9.0 (1.6)	0.58 (0.06)	29.9 (3.4)*
10–19 teeth	310.5 (5.2)	8.9 (1.3)	0.49 (0.04)	28.3 (2.6)*
>19 teeth[¶]	295.7 (3.3)	7.2 (1.2)	0.41 (0.01)	21.6 (1.6)
Gingival bleeding				
19–100% Extent	310.3 (4.6)	10.1 (2.1)	0.52 (0.04)	31.7 (4.7)
0–18% Extent[¶]	298.3 (3.4)	7.2 (1.0)	0.43 (0.02)	22.2 (1.5)
Attachment loss 3 mm				
31–100% Extent	313.4 (3.7)	8.8 (1.1)	0.52 (0.03)	27.9 (2.3)*
0–30% Extent[¶]	296.9 (3.5)	7.3 (1.2)	0.42 (0.02)	22.4 (1.6)

Table 2. (Contd.)

Characteristic	Fibrinogen‡ mean (SE)	High fibrinogen§ (SE) %	CRP‡ mean (SE)	High CRP§ % (SE)
Periodontal disease present¶¶				
Yes	319.1 (8.3)	11.6 (2.3)*	0.51 (0.04)	25.9 (3.3)
No¶	297.2 (2.6)	7.0 (0.8)	0.43 (0.01)	23.3 (1.6)
Periodontal disease extent‖‖				
High	321.5 (7.8)	10.1 (2.2)	0.52 (0.06)	25.7 (5.6)
Lower¶	299.4 (3.0)	7.6 (0.9)	0.44 (0.01)	23.6 (1.6)

*$P < 0.05$ compared with the reference category (pairwise comparison for dichotomous CRP and Fibrinogen only).
†NHANES III phase 2 sample only.
‡In units of mg/dl.
§Fibrinogen high value: > 400 mg/dl ($N = 320$); C-reactive protein high value: > 0.40 mg/dl ($N = 880$).
¶Reference category.
‖Other potential inflammatory conditions: creatinine levels indicate renal failure, reports taking oral estrogen, or reports having osteo/rheumatoid arthritis.
**Total cholesterol-HDL ratio – high value: in the upper fifth-quintile.
††Elevated Aa: titre level ⩾ 156 U.
§§Elevated Pg: titre level ⩾ 168 U.
¶¶Periodontal disease defined as having at least 1site with LOA ⩾ 3 mm and PD ⩾ 4 mm.
‖‖Periodontal disease extent defined as having LOA ⩾ 3 mm and PD ⩾ 4 mm at the same site in 15% or more of the sites.
HDL, total cholesterol-high-density lipoprotein; CRP, C-reactive protein; BMI, body mass index; NHANES III, third National Health and Nutrition Examination Survey; LOA, loss of attachment; PD, pocket depth.

women, being non-Hispanic black, having other potential inflammatory conditions, being obese or overweight, and having elevated *P. gingivalis* antibody titres remained essentially similar as in the previous model. However, dentate status was no longer independently associated with high CRP levels.

Discussion

In a national sample representative of more than 62 million Americans aged 40 years and older, we examined the relationship between serum IgG antibodies to two major periodontal pathogens, *A. actinomycetemcomitans* and *P. gingivalis*, and two acute phase proteins, CRP and fibrinogen, both of which have been shown to be predictors of CVD. Our results indicate that an elevated IgG titre to *P. gingivalis* is independently associated with high serum CRP. In contrast, titres to *A. actinomycetemcomitans* were not associated with CRP levels, and neither titre was associated with plasma fibrinogen. The association of antibody response to *P. gingivalis* and

Table 3. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for high plasma Fibrinogen among adults aged 40 years or older: United States 1991–94†

Characteristic	Approach A		Approach B		Approach C	
	Model 1 OR (CI)	Model 2 OR (CI)	Model 1 OR (CI)	Model 2 OR (CI)	Model 1 OR (CI)	Model 2 OR (CI)
Age						
70+ years	1.98 (0.75, 5.22)		2.13 (0.83, 5.46)		2.18 (0.86, 5.54)	
55–69 years	1.24 (0.63, 2.45)	–	1.30 (0.67, 2.51)	–	1.32 (0.69, 2.50)	–
40–54 years‡	1.00		1.00		1.00	
Sex						
Women	1.68 (1.09, 2.60)	1.50 (1.06, 2.11)	1.70 (1.10, 2.61)	1.50 (1.06, 2.11)	1.82 (1.22, 2.73)	1.57 (1.13, 2.19)
Men‡	1.00	1.00	1.00	1.00	1.00	1.00
Race/ethnicity						
Mexican American	0.85 (0.40, 1.79)		0.83 (0.38, 1.81)		0.80 (1.13, 2.19)	
Non-Hispanic black	1.73 (0.89, 3.33)	–	1.79 (0.95, 3.38)	–	1.65 (0.86, 3.18)	–
Non-Hispanic white‡	1.00		1.00		1.00	
Education attainment						
Not completed high school	2.00 (1.21, 3.29)	1.99 (1.24, 3.21)	2.11 (1.19, 3.75)	1.99 (1.24, 3.21)	1.99 (1.17, 3.37)	1.87 (1.16, 3.02)
Completed high school	1.50 (1.09, 2.06)	1.36 (0.95, 1.94)	1.55 (1.12, 2.13)	1.36 (0.95, 1.94)	1.49 (1.08, 2.05)	1.30 (0.91, 1.87)
Some college‡	1.00	1.00	1.00	1.00	1.00	1.00
Cigarette smoking						
Current smoker	1.13 (0.64, 2.00)		1.16 (0.65, 2.08)		1.07 (0.61, 1.88)	
Former smoker	1.30 (0.76, 2.17)	–	1.32 (0.78, 2.23)	–	1.30 (0.77, 2.19)	–
Never smoked‡	1.00				1.00	
Other potential inflammatory conditions§						
Yes	1.00 (0.58, 1.71)	–	1.01 (0.58, 1.70)	–	0.98 (0.57, 1.69)	–
No‡	1.00		1.00			
Diagnosed diabetic						
Yes	1.49 (0.95, 2.34)	1.69 (1.09, 2.61)	1.55 (0.95, 2.53)	1.69(1.09, 2.61)	1.52 (0.94, 2.46)	1.65 (1.07, 2.56)
No‡	1.00	1.00	1.00	1.00	1.00	1.00
Permanent teeth present						
1–9 teeth			0.85 (0.42, 1.72)		0.90 (0.45, 1.79)	
10–19 teeth	NA	NA	0.72 (0.41, 1.25)	–	0.71 (0.42, 1.20)	–
20+ teeth‡			1.00		1.00	

Table 3. (Contd.)

Characteristic	Approach A		Approach B		Approach C	
	Model 1 OR (CI)	Model 2 OR (CI)	Model 1 OR (CI)	Model 2 OR (CI)	Model 1 OR (CI)	Model 2 OR (CI)
Periodontal disease present[¶]						
Yes	NA	NA	NA	NA	1.92 (1.19, 3.08)	1.64 (1.10, 2.44)
No[‡]					1.00	1.00
Aa Elevated titre[‖]						
Yes	1.22 (0.39, 3.85)	–	1.23 (0.39, 3.85)	–	1.20 (0.41, 3.51)	–
No[‡]	1.00		1.00		1.00	
Pg Elevated titre[**]						
Yes	0.86 (0.42, 1.73)	–	0.85 (0.43, 1.72)	–	0.77 (0.38, 1.58)	–
No[‡]	1.00		1.00		1.00	

[†]NHANES III phase 2 sample only.

[‡]Reference category.

[§]Other potential inflammatory conditions: creatinine levels indicate renal failure, reports taking oral estrogen, or reports having osteo/rheumatoid arthritis.

[¶]Periodontal Disease defined as having at least one site with LOA $\geqslant$ 3 mm and PD $\geqslant$ 4 mm.

[‖]Elevated Aa: titre level $\geqslant$156 U.

[**]Elevated Pg: titre level $\geqslant$168 U.

[*]Models produced in SUDAAN: Fibrinogen high value: $>$400 mg/dl.

NA, not available.

–, covariant not included in this model (removed for non-significance: $p > 0.05$).

Model 1: produced with all covariates in the model (full model).

Model 2: the most parsimonious model (final model).

HDL, total cholesterol-high-density lipoprotein; CRP, C-reactive protein; BMI, body mass index; NHANES III, third National Health and Nutrition Examination Survey; LOA, loss of attachment; PD, pocket depth; OR, odds ratios; CI, confidence intervals.

Table 4. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for high serum CRP among adults aged 40 years or older: United States 1991–94[†]

Characteristic	Approach A		Approach B		Approach C	
	Model 1 OR (CI)	Model 2 OR (CI)	Model 1 OR (CI)	Model 2 OR (CI)	Model 1 OR (CI)	Model 2 OR (CI)
Age						
70+years	1.40 (0.89, 2.21)		1.39 (0.85, 2.26)		1.32 (0.81, 2.17)	
55–69 years	1.16 (0.85, 1.56)	–	1.15 (0.84, 1.57)	–	1.13 (0.83, 1.52)	–
40–54 years[‡]	1.00		1.00		1.00	
Sex						
Women	2.25 (1.49, 3.40)	2.00 (1.39, 2.88)	2.25 (1.50, 3.37)	2.06 (1.41, 3.00)	2.30 (1.55, 3.41)	2.17 (1.49, 3.14)
Men[‡]	1.00	1.00	1.00	1.00	1.00	1.00
Race/ethnicity						
Mexican American	1.00 (0.74, 1.36)		1.01 (0.75, 1.35)	1.12 (0.86, 1.46)	1.01 (0.75, 1.35)	1.10 (0.85, 1.44)
Non-Hispanic black	1.25 (0.88, 1.78)	–	1.25 (0.88, 1.78)	1.41 (1.04, 1.92)	1.24 (0.88, 1.77)	1.42(1.06, 1.91)
Non-Hispanic white[‡]	1.00			1.00	1.00	1.00
Education attainment						
Not completed high school	1.35 (0.99, 1.87)	1.54 (1.11, 2.12)	1.33 (0.96, 1.84)		1.30 (0.95, 1.78)	
Completed high school	1.49 (1.07, 2.07)	1.53 (1.05, 2.22)	1.48 (1.07, 2.04)	–	1.47 (1.07, 2.03)	–
Some college[‡]	1.00 1.00		1.00		1.00	
Cigarette smoking						
Current smoker	1.90 (1.25, 2.88)		1.89 (1.24, 2.86)		1.80 (1.17, 2.77)	
Former smoker	1.17 (0.80, 1.72)	–	1.17 (0.80, 1.71)	–	1.16 (0.79, 1.69)	–
Never smoked[‡]	1.00		1.00		1.00	
Other potential inflammatory conditions[§]						
Yes	1.38 (1.02, 1.87)	1.43 (1.07, 1.91)	1.38 (1.02, 1.86)	1.41 (1.06, 1.88)	1.38 (1.02, 1.85)	1.41 (1.06, 1.86)
No[‡]	1.00	1.00	1.00	1.00	1.00	1.00
BMI level						
$\geqslant$30	4.14 (3.04, 5.63)	3.85 (2.87, 5.16)	4.13 (3.05, 5.60)	3.88 (2.89, 5.21)	4.19 (3.09, 5.68)	4.07 (3.05, 5.43)
25 to $<$30	2.12 (1.61, 2.79)	2.07 (1.61, 2.65)	2.12 (1.60, 2.79)	2.07 (1.62, 2.66)	2.13 (1.61, 2.82)	2.13 (1.65, 2.74)
$<$25[‡]	1.00	1.00	1.00	1.00	1.00	1.00
Diagnosed diabetic						
Yes	1.54 (0.81, 2.93)	–	1.53 (0.81, 2.92)	–	1.51 (0.79, 2.90)	–
No[‡]	1.00		1.00		1.00	

Table 4. (Contd.)

Characteristic	Approach A		Approach B		Approach C	
	Model 1 OR (CI)	Model 2 OR (CI)	Model 1 OR (CI)	Model 2 OR (CI)	Model 1 OR (CI)	Model 2 OR (CI)
Permanent teeth present						
1–9 Teeth			1.07 (0.76, 1.50)	1.39 (1.09, 1.86)	1.00 (0.65, 1.47)	
10–19 Teeth	NA	NA	1.03 (0.71, 1.48)	1.25 (0.88, 1.78)	1.00 (0.67, 1.47)	–
20+teeth‡			1.00	1.00	1.00	
Attachment loss 3 mm						
31–100% Extent	NA	NA	NA	NA	1.26 (0.85, 1.88)	1.58 (1.19, 2.08)
0–30% extent‡					1.00	1.00
Aa elevated antibody¶						
Yes	1.66 (0.90, 3.04)	–	1.66 (0.90, 3.04)	–	1.65 (0.89, 3.03)	–
No‡	1.00		1.00		1.00	
Pg elevated antibody‖						
Yes	1.69 (1.18, 2.42)	1.63(1.15, 2.32)	1.69 (1.18, 2.42)	1.69 (1.18, 2.41)	1.63(1.15, 2.31)	1.58 (1.12, 2.23)
No‡	1.00	1.00	1.00	1.00	1.00	1.00

†NHANES III Phase 2 sample only.

‡Reference category.

§Other potential inflammatory conditions: creatinine levels indicate renal failure, reports taking oral estrogen, or reports having osteo/rheumatoid Arthritis.

¶Elevated Aa: titre level $\geqslant 156$ U.

‖ Elevated Pg: titre level $\geqslant 168$ U.

*Models produced in SUDAAN: C-reactive protein high value: > 0.40 mg/dl

NA, not available.

–, Covariant not included in this model (removed for non-significance: $p > 0.05$).

Model 1: produced with all covariates in the model (full model).

Model 2: the most parsimonious model (final model).

HDL, total cholesterol-high-density lipoprotein; CRP, C-reactive protein; BMI, body mass index; NHANES III, third National Health and Nutrition Examination Survey.

high CRP provides support to the notion that periodontal infections may contribute to systemic inflammation and thereby to atherosclerosis and CVD.

We explored the association between acute phase proteins and serum antibodies to periodontal bacteria by means of three different modelling approaches, each based on a different assumption dependent upon the availability of basic dental data and clinical periodontal measures. In addition to testing our main hypothesis, this analytical strategy allowed us to determine whether the intensity of the antibody responses to infecting periodontal bacteria conveys information beyond the one provided by the clinical periodontal status alone. As stated in the introduction, the majority of studies investigating the association of periodontal disease to systemic health outcomes have employed clinical measures of periodontitis as exposures. Serology to periodontal microbiota represents an alternative marker of periodontal infection, and the level of these antibody responses may help in the differentiation between states of mere bacterial colonization and infection.

Earlier studies by our group (Papapanou et al. 2001, Papapanou et al. 2004) and others (Pussinen et al. 2002) have suggested that elevated titres to *A. actinomycetemecomitans* and *P. gingivalis* are suggestive of more extensive and severe periodontal disease. This notion is corroborated by the present findings, especially in the case of high *P. gingivalis* titre. As shown in Table 1, the proportion of subjects with a high titre to *P. gingivalis* increased from 7.7%, in subjects with 0–15% extent of attachment loss of $\geqslant 3$ mm, to 20.3%, in subjects with an extent of 46–100%. Similarly, a high titre to *P. gingivalis* was prevalent in 36.2% of the subjects with LOA of $\geqslant 3$ mm and concomitant PD of $\geqslant 4$ mm in at least 15% of their sites, but in only 10% of the subjects with lower extent. Previous reports using these data have suggested that serum IgG antibody response to *P. gingivalis* is associated with increasing periodontal disease severity (Hyman et al. 2002). The relationship between a high titre to *A. actinomycetemecomitans* and periodontal disease extent was less pronounced and did not follow the dose–response pattern of the *P. gingivalis* titre.

The data shown in Table 4 confirm that both a high extent of attachment loss, representing a widespread periodontitis, and a high titre to *P. gingivalis* were independently associated with elevated CRP levels. An effect of periodontitis, assessed by clinical measures, on high CRP level has been documented in a number of studies (Ebersole et al. 1997, Loos et al. 2000, Noack et al. 2001, Saito et al. 2003), including two earlier analyses of the NHANES III database (Slade et al. 2000, Wu et al. 2000b). A similar relationship between advanced periodontitis and plasma fibrinogen has also been reported (Kweider et al. 1993, Wu et al. 2000b). Our data indicate that subjects with elevated titres to *P. gingivalis* are more likely to have high CRP levels compared with those with lower titres to *P. gingivalis*. However, subjects with elevated titres to *A. actinomycetemcomitans* and *P. gingivalis* did not show significantly higher fibrinogen levels (Table 2). High CRP was significantly more prevalent in subjects with extensive rather than minimal tooth loss and with high *versus* low extent of attachment loss. Persons with prevalent periodontitis, according to the composite definition used, were more likely to have higher fibrinogen levels compared with those subjects without periodontitis (11.6% *versus* 7.0%, Table 2). Interestingly, a reduction of CRP levels after successful periodontal therapy has been recently reported (Mattila

et al. 2002, Iwamoto et al. 2003, D'Aiuto et al. 2004), although a number of studies have failed to detect such an effect (Ide et al. 2003, Yamazaki et al. 2005).

In the existing literature, information on the association of serum titres to periodontal microbiota and acute phase protein levels is limited and is based on small subject samples. Serum antibodies to six periodontal species and CRP levels were investigated in a subject sample of 86 dentate persons with haemodialysis (Rahmati et al. 2002), and a significant association between IgG to *P. gingivalis* and CRP was shown to persist after adjustment for several potential sources of systemic inflammation. Based on data from 69 subjects, Craig et al. (2003) similarly reported a statistically significant positive association between CRP and IgG to *P. gingivalis* but not to titres against five other periodontal species including *A. actinomycetemcomitans*.

A number of recent studies originating from a single research group in Finland have examined the relationship of serum responses to *A. actinomycetemcomitans* and *P. gingivalis* and subclinical atherosclerosis, CVD, and stroke. Pussinen et al. (2003) reported that coronary heart disease (CHD) was more common among dentate subjects who were seropositive for *P. gingivalis* when compared with those seronegative. Moreover, CHD was more prevalent in subjects with a high combined antibody response to both *A. actinomycetemcomitans* and *P. gingivalis* than those with a low antibody response. In a prospective follow-up study, the same authors examined IgA antibodies to *A. actinomycetemcomitans* and *P. gingivalis* and reported that high titres doubled the relative risk for an acute myocardial infarction (Pussinen et al. 2005). Findings from another small case–control study (Pussinen et al. 2004b) reported a positive association between serum IgA to *P. gingivalis* and myocardial infarction; however, sera IgA to *A. actinomycetemcomitans* and IgG to both *A. actinomycetemcomitans* and *P. gingivalis* were found to be unrelated to clinical events. Finally, in a prospective study (Pussinen et al. 2004a), IgA seropositivity to *A. actinomycetemcomitans* conferred an odds ratio of 1.6 for stroke in subjects with no prior history, and IgA seropositivity to *P. gingivalis* an odds ratio of 2.6 for secondary stroke, although both odds ratio estimates approached, but did not reach, statistical significance.

Collectively, the above findings appear to corroborate the value of serology to periodontal microbiota, especially *P. gingivalis*, in the study of the association between periodontal infections, systemic inflammation, atherosclerosis, and resulting clinical events. A recent study has demonstrated that colonization by a cluster of four periodontal pathogens (*P. gingivals, T. forsythia, T. denticola*, and *A. actinomycetemcomitans*) at high levels was independently associated with increased intima-media thickness (Desvarieux et al. 2005).

A limitation of our study is the use of data obtained from a cross-sectional study design to examine indicators for increased levels of CRP and fibrinogen, which prevents a definitive exploration of causality. Additionally, the clinical periodontal status indicators used in our study were derived from a partial-mouth examination. The use of partial recording may underestimate periodontal disease levels, and underreporting of disease may also underestimate the magnitude of any observed association (Kingman et al. 1988, Hunt & Fann 1991). Nevertheless, the use of a nationally representative sample, not selected on the basis of multiple risk indicators or other potential confounding factors, is an important study design strength.

The potential for collinearity among the oral health explanatory variables (periodontal antibodies, dentate status, and periodontal disease measures) was investigated and found to be moderate. The modest correlation between exposure (periodontal antibody) and dentate status must in part be ascribed to the established effect of dental caries to tooth loss.

The assessment of CRP during NHANES III was performed by means of a medium sensitivity assay (Tuengler et al. 1988, Wener et al. 2000), which has a low detection limit of 0.2–0.3 mg/dl. Since then, high sensitivity assays have become available and are now recommended as the preferable assessment for CVD risk (Pearson et al. 2003, Ridker 2003, Yeh & Willerson 2003). However, a recent study (Clarke et al. 2005) comparing the impact of differing CRP assay methods on cardiovascular risk assessments suggested that earlier assays should still be regarded as valid. Findings from this study demonstrated a high correlation by quartile rank between medium sensitivity and high sensitivity assays as well as similar predictive values for death and myocardial infarction.

Elevated CRP is associated with vascular disease risk, developing type 2 diabetes, obesity, and metabolic syndrome (Hackam & Anand 2003, Aronson et al. 2004). Recently, there have been suggestions promoting the exploration of an ''inflammation hypothesis'' by testing the pharmacotherapeutic potential of CRP suppression on the reduction of arterial inflammation (Bhatt & Topol 2002, Biasucci 2004). Although our study design prevents examination for causality, our findings demonstrating an association between high serum IgG antibodies to *P. gingivalis* and CRP could become an important consideration for the design of future studies. As research investigating markers of chronic inflammation and related issues continues to expand, the incorporation of serological markers of periodontal infection in studies may help differentiate between states of mere bacterial colonization and infection, and may further increase our understanding of the nature of the periodontitis-CVD association.

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Clinical significance

High levels of serum antibodies to key periodontal bacteria are thought to reflect the intensity of the periodontal infection. In this work, we demonstrate in a nationally representative sample that high titres to *P. gingivalis* are independently associated with high levels of CRP, an acute phase protein that signifies the presence of systemic inflammation. Importantly, a high titre to *P. gingivalis* was related to high CRP levels even when the clinical periodontal status was accounted for, suggesting that an elevated *P. gingivalis* titre is of value in the assessment of the systemic effects of periodontitis.

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