



The association between clinically determined periodontal disease and prostate-specific antigen concentration in men without prostate cancer: the 2009–2010 National Health and Nutrition Examination Survey

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Abstract

Purpose We evaluated the association between clinically assessed periodontal disease and serum prostate-specific antigen (PSA) concentration in men without a prostate cancer diagnosis in a US nationally representative sample of non-institutionalized men.

Methods Included were 1263 men aged ≥ 40 years who participated in the National Health and Nutrition Examination Survey in 2009–2010. Measurements of periodontal health and tooth count were used to define periodontal disease severity (no, mild, moderate, severe) and edentulism. Linear and logistic regressions were used to estimate the association of periodontal disease severity and edentulism with PSA concentration and elevated PSA, respectively.

Results Adjusting for age and other factors including race, body mass index, and education, the natural logarithm of PSA concentration did not change with increasing severity (mild -0.20 , 95% confidence interval [CI] -0.34 to -0.05 ; moderate -0.12 , 95% CI -0.26 to 0.01 ; severe -0.16 , 95% CI -0.43 to 0.12 ; edentulism -0.16 , 95% CI -0.35 to 0.04 ; P -trend 0.13) compared with dentate men without periodontal disease. Although the multivariable-adjusted ORs of elevated PSA were not statistically significant, participants with more severe periodontal disease were less likely to have PSA > 2.0 and > 2.5 ng/mL, but more likely to have PSA > 4.0 ng/mL, compared to dentate men without periodontal disease. Similar non-significant associations with PSA were observed when comparing edentulous men to dentate men without periodontal disease.

Conclusions In this US nationally representative sample, men with periodontal disease did not have higher serum PSA and were not more likely to have clinically elevated PSA after taking into account age and other factors, contrary to the hypothesis. This study suggests that periodontal disease does not notably affect the specificity of PSA for prostate cancer screening.

Keywords Periodontal disease · PSA · Men · NHANES

Introduction

The prostate-specific antigen (PSA) test has been routinely used for prostate cancer screening in the US since the early 1990s. A serum PSA concentration > 4 ng/mL is generally considered an indication for prostate biopsy to make or exclude the diagnosis of prostate cancer, although lower cut-off points are also used. The serum PSA test has suboptimal specificity because PSA concentration can be elevated in non-malignant conditions such as symptomatic and asymptomatic prostatitis [1–3]. Thus, the results of PSA-based prostate cancer screening could be misleading and cause unnecessary prostate biopsy in men with pro-inflammatory health states and exposures.

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Understanding the array of health states and exposures that influence serum PSA is needed to aid in clinical decision-making for screening and for performing a prostate biopsy given a PSA test result. One possible health state is periodontal disease. Periodontal disease is a chronic inflammatory condition caused by bacterial infection of the supporting gum and bone tissues around the teeth [4, 5]. Since both periodontal disease and category I and II prostatitis have Gram-negative bacteria as etiologic agents [6], several studies have investigated the association between periodontal disease and PSA among men who underwent prostate biopsy or had chronic periodontal disease [6–8]. However, the results are conflicting and the sample sizes are very small, and none has investigated the association in a general population of men in the age range for prostate cancer screening.

Given that 42% of dentate (possessing natural teeth) US adults have periodontitis and given the routine use of PSA-based prostate cancer screening [9], the influence of periodontal disease on PSA concentration needs to be investigated. Using the 2009–2010 National Health and Nutrition Examination Survey (NHANES), a US nationally representative sample of non-institutionalized Americans, we evaluated the association between clinically assessed periodontal disease and PSA in men aged 40 and older without a prostate cancer diagnosis. To inform etiology, we examined severity of periodontal disease and edentulism in relation to the distribution of PSA as continuous variable. To assess clinical import, we examined their relation with higher (versus lower) PSA concentration that may lead to a biopsy recommendation. Given the age of our study population, we expected that the prevalence of periodontal disease would be higher than the overall national prevalence of periodontal disease. We hypothesized the men with periodontal disease, especially severe, would have a higher serum PSA concentration and be more likely to have clinically elevated PSA.

Methods

Study population

NHANES is a series of cross-sectional studies conducted by the National Center for Health Statistics of the US Centers for Disease Control and Prevention [10]. By design, each cycle of NHANES is representative of the total civilian non-institutionalized population of adults and children aged 2 months or older in the USA. It utilizes a multistate stratified probability sample and includes an oversampling of Hispanics, non-Hispanic blacks, and the elderly to allow for more precise estimates in these subgroups. Unbiased national estimates of health and nutritional characteristics

can be produced for each cycle. This analysis included men from the cycle of 2009–2010.

Measurement and classification of periodontal disease

Participants aged ≥ 30 years were eligible for periodontal examination if they had at least one natural tooth and did not meet any of the health exclusion criteria. All periodontal examinations were conducted in a mobile examination center by trained examiners who were registered dental hygienists. All dental examiners were trained and calibrated by the survey's reference examiner. Examiners made two measurements at each periodontal site: gingival recession and probing pocket depth (PD). Measurements were made at six sites per tooth (mesio-, mid-, and disto-buccal; mesio-, mid-, and disto-lingual) for all teeth, excluding third molars. A count of all teeth was done. Data were recorded directly into a NHANES oral health data management program that calculated attachment loss (AL) as the difference between probing pocket depth and recession. Details are reported in [11].

We classified the men into five categories, no periodontitis, mild periodontitis, moderate periodontitis, severe periodontitis, and edentulism. The first 4 categories were defined using the Centers for Disease Control/American Academy of Periodontology case definitions for surveillance of periodontitis [12] among men with at least one natural tooth. No periodontitis was defined as no evidence of mild, moderate, or severe periodontitis. Mild periodontitis was defined as ≥ 2 interproximal sites with $AL \geq 3$ mm, and ≥ 2 interproximal sites with $PD \geq 4$ mm (not on the same tooth) or 1 site with $PD \geq 5$ mm. Moderate periodontitis was defined as ≥ 2 interproximal sites with $AL \geq 4$ mm (not on the same tooth), or ≥ 2 interproximal sites with $PD \geq 5$ mm (not on the same tooth). Severe periodontitis was defined as ≥ 2 interproximal sites with $AL \geq 6$ mm (not on the same tooth) and ≥ 1 interproximal site with $PD \geq 5$ mm. Finally, edentulism was defined as not having any natural teeth remaining.

Measurement of serum PSA concentration and classification of elevated PSA

As part of the NHANES 2009–2010 protocol, serum total PSA concentration was measured in men who were ≥ 40 years of age, who consented, and who did not have a prostate cancer diagnosis, recent biopsy in past month, recent examination in past week, or cystoscopy in past month, or current infection or inflammation of the prostate. Serum total PSA concentration was measured using the Beckman Access Immunoassay System with the Hybritech Total PSA Assay (Beckman Coulter, Fullerton, CA). The lower detection limit for total serum PSA was 0.10 ng/mL. Where the

concentration was below the limit of detection ($n=9$ men), NHANES substituted the detection limit divided by the square root of two. We categorized serum PSA concentration into normal and elevated concentrations with cutpoints at 4.0, 2.5, and 2.0 ng/mL. These cutpoints were selected because 4.0 ng/mL is the most commonly used cutpoint for prostate biopsy recommendation and they yield different prostate cancer detection rates [13].

Measurement of covariates

Age, race/ethnicity, education, income, cigarette smoking, and history of a diagnosis of type II diabetes mellitus were assessed by standardized in-home interview. Body height, body weight, fasting glucose, and glycated hemoglobin were measured during a mobile medical examination center visit. We categorized race/ethnicity as non-Hispanic white, non-Hispanic black, Hispanic (combined Mexican–American and other Hispanic), and other. Education was categorized as less than high school, high school, and above high school. Income was categorized as annual family income < \$25,000, \$25,000–\$74,999, and > \$74,999. Cigarette smoking was categorized as never (men who smoked fewer than 100 cigarettes during their lifetime), former (men who smoked at least 100 cigarettes in their lifetime and reported that they now smoke “not at all”), and current smokers (men who smoked at least 100 cigarettes in their lifetime and reported they now smoke “every day” or “some days”). We categorized diabetes status as non-diabetic (no diagnosis of diabetes from a doctor), pre-diabetic (no diagnosis of diabetes from a doctor, and fasting glucose between 100 and 125 mg/dL or glycated hemoglobin between 5.7% and 6.4%), and diabetic (diagnosis of diabetes from a doctor, or fasting glucose > 125 mg/dL, or glycated hemoglobin > 6.4%). Body mass index (BMI) was calculated from weight and height (kg/m^2).

Statistical analysis

A total of 1429 men aged ≥ 40 years had both periodontal disease status and PSA measured. We excluded 147 men with missing characteristics (height, weight, income, education, smoking status, diabetes status) and 19 men with extreme BMI (< 18.5 or > 50 kg/m^2). Thus, 1263 men were included in the analysis.

Linear regression was used to estimate the association of periodontal disease severity and edentulism with serum PSA concentration adjusting for age (continuous), race/ethnicity (categories), BMI (continuous), and education (categories), income (categories), cigarette smoking (categories), and diabetes (categories). Because serum PSA concentration had a highly right skewed distribution, we modeled the natural logarithm of PSA. We used logistic regression to

the estimate odds ratios (ORs) and 95% confidence intervals (CIs) of periodontal disease severity and edentulism with elevated PSA (binary variable) adjusting for the same covariates as in the linear regression. In sensitivity analysis, we excluded men who ever had periodontal treatment given that they may have been cured and no longer have active periodontal disease. We excluded men with PSA concentration > 95th percentile because their elevation may be due to prostate cancer or benign prostatic hyperplasia (BPH) nodules, which may have made it more difficult to isolate any influence of periodontal disease on PSA independent of any effects of periodontal disease on prostate cancer or BPH. All statistical analyses were performed with Stata version 14 (Stata Corp., TX, USA). Statistical tests were two-sided, and a P value of less than 0.05 was considered to be statistically significant.

Results

Characteristics of participants

Characteristics of the 1263 men are presented in Table 1, overall and by categories of periodontal disease severity and edentulism. Overall, the men had a mean age of 55.4 years and 76.1% were non-Hispanic white. Mean BMI was 29.1 kg/m^2 and geometric mean PSA was 0.97 ng/mL. 57.5% were pre-diabetic or diabetic, 41.2% were former or current smokers, 42.5% had annual family income > \$74,999, and 59.3% had above a high school education. 8.2% of men had mild, 39.6% had moderate, and 18.1% had severe periodontal disease, and 8.8% were edentulous. Generally, men with more severe periodontal disease were more likely to be older, diabetic, and former or current smokers, and to have lower income and education level.

Association between periodontal disease and PSA

Not taking into account age or other potentially confounding factors, generally, men with more severe periodontal disease or with edentulism had higher mean PSA (Table 1), but not higher geometric mean PSA.

After adjusting for age and race/ethnicity and after further adjusting for BMI, education, income, cigarette smoking, and diabetes, the natural logarithm of PSA concentration did not change with increasing periodontal disease severity compared with dentate men without periodontal disease (Table 2). Compared with dentate men without periodontal disease, we could not rule out that men with periodontal disease, irrespective of severity, had lower PSA than those without periodontal disease; this inverse association was statistically significant for mild periodontal disease.

Table 1 Weighted characteristics of participants across periodontal disease categories, men in NHANES 2009–2010^a

	Overall (<i>n</i> = 1263)	No PD (<i>n</i> = 320)	Mild (<i>n</i> = 103)	Moderate (<i>n</i> = 500)	Severe (<i>n</i> = 229)	Edentulism (<i>n</i> = 111)
Total PSA, geometric mean (95% CI), ng/mL	0.97 (0.93, 1.02)	0.97 (0.87, 1.07)	0.79 (0.67, 0.94)	1.01 (0.93, 1.10)	0.96 (0.78, 1.17)	1.16 (0.96, 1.39)
Total PSA, mean (SD), ng/mL	1.44 (1.91)	1.26 (0.99)	1.04 (1.08)	1.58 (2.25)	1.51 (3.00)	1.97 (3.03)
PSA > 4 ng/mL (%)	5.28	2.77	2.02	7.58	5.66	10.10
PSA > 2.5 ng/mL (%)	12.3	8.42	6.82	16.5	11.8	12.3
PSA > 2.0 ng/mL (%)	16.8	13.5	11.1	20.3	16.0	24.0
Age, mean (SD), years	55.4 (11.1)	51.8 (8.18)	51.7 (8.65)	57.8 (11.8)	56.2 (11.5)	64.7 (13.5)
BMI, mean (SD), kg/m ²	29.1 (5.42)	29.0 (4.43)	29.4 (4.43)	29.4 (5.99)	28.8 (6.48)	28.9 (6.35)
Diabetes (%)						
No diabetes	42.5	49.3	50.8	39.3	35.3	25.9
Pre-diabetes	39.7	38.5	38.1	39.4	44.7	40.0
Diabetes	17.8	12.2	11.1	21.3	20.0	34.1
Race (%)						
Non-Hispanic white	76.1	85.6	80.1	73.0	55.0	82.3
Non-Hispanic black	8.71	4.33	6.71	11.0	15.2	8.41
Hispanic	10.9	6.86	12.7	11.8	19.3	6.96
Other	4.28	3.22	0.51	4.18	10.5	2.30
Cigarette smoking status (%)						
Never	48.8	67.4	54.2	40.1	33.7	19.8
Former	33.7	26.7	33.3	38.3	32.7	49.2
Current	17.5	5.89	12.4	21.6	33.6	31.0
Income (%), dollars						
<25,000	17.2	9.11	12.9	16.9	33.1	35.7
25,000–74,999	40.3	27.2	34.2	50.6	45.7	51.3
>74,999	42.5	63.7	52.9	32.5	21.2	12.9
Education (%)						
<High school	17.8	7.24	10.8	18.6	31.9	51.3
High school	23.0	17.7	22.4	24.9	30.0	26.2
>High school	59.3	75.1	66.8	56.5	38.1	22.5

^aPSA prostate-specific antigen, CI confidence interval, SD standard deviation, BMI body mass index

Table 2 Association of periodontal disease severity and edentulism with serum prostate-specific antigen concentration, men in NHANES 2009–2010^a

	No PD (<i>n</i> = 320)	Mild (<i>n</i> = 103)	Moderate (<i>n</i> = 500)	Severe (<i>n</i> = 229)	Edentulism (<i>n</i> = 111)	<i>P</i> -trend ^d
ln(PSA) Coefficients (95% CI)						
Model 1 ^b Reference		−0.20 (−0.36, −0.04)	−0.14 (−0.28, 0.00)	−0.16 (−0.45, 0.13)	−0.19 (−0.35, −0.02)	0.16
Model 2 ^c Reference		−0.20 (−0.34, −0.05)	−0.12 (−0.26, 0.01)	−0.16 (−0.43, 0.12)	−0.16 (−0.35, 0.04)	0.13

^aPD periodontal disease, PSA prostate-specific antigen, CI confidence interval

^bModel 1 adjusted for age in years (continuous) and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other)

^cModel 2 adjusted for age in years (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), body mass index (continuous), annual family income (<\$25,000, \$25,000–\$74,999, >\$74,999), education (<high school, high school, >high school), smoking (never, former, current), and diabetes (non-diabetic, pre-diabetic, diabetic)

^d*P* for trend for periodontal disease severity in dentate men

Compared to dentate men without periodontal disease, the multivariable-adjusted OR of elevated PSA did not change with increasing periodontal disease severity, regardless of

the cut-off value of elevated PSA used (Table 3). Although the associations were not statistically significant, participants with severe periodontal disease were less likely to

Table 3 Association of periodontal disease severity and edentulism with elevated serum prostate-specific antigen, men in NHANES 2009–2010^a

	No PD (<i>n</i> = 320)	Mild (<i>n</i> = 103)	Moderate (<i>n</i> = 500)	Severe (<i>n</i> = 229)	Edentulism (<i>n</i> = 111)	<i>P</i> -trend ^d
Odds ratio (95% CI)						
PSA > 2 ng/mL	59	11	122	46	33	
Model 1 ^b	Reference	0.78 (0.31, 1.96)	0.95 (0.53, 1.70)	0.82 (0.29, 2.34)	0.69 (0.29, 1.67)	0.69
Model 2 ^c	Reference	0.76 (0.32, 1.82)	0.95 (0.52, 1.75)	0.75 (0.27, 2.11)	0.65 (0.23, 1.79)	0.56
PSA > 2.5 ng/mL	40	7	101	35	29	
Model 1 ^b	Reference	0.80 (0.23, 2.78)	1.17 (0.58, 2.37)	0.87 (0.41, 1.83)	0.77 (0.36, 1.66)	0.91
Model 2 ^c	Reference	0.76 (0.23, 2.50)	1.12 (0.55, 2.27)	0.75 (0.38, 1.51)	0.67 (0.34, 1.31)	0.85
PSA > 4.0 ng/mL	14	4	51	16	16	
Model 1 ^b	Reference	0.77 (0.19, 3.17)	1.34 (0.72, 2.52)	1.10 (0.56, 2.17)	0.96 (0.30, 3.13)	0.45
Model 2 ^c	Reference	0.85 (0.22, 3.25)	1.58 (0.82, 3.04)	1.28 (0.60, 2.73)	1.27 (0.42, 3.82)	0.15

^aPD periodontal disease, PSA prostate-specific antigen, CI confidence interval

^bModel 1 adjusted for age in years (continuous) and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other)

^cModel 2 adjusted for age in years (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), body mass index (continuous), annual family income (<\$25,000, \$25,000–\$74,999, >\$74,999), education (<high school, high school, >high school), smoking (never, former, current), and diabetes (non-diabetic, pre-diabetic, diabetic)

^d*P* for trend for periodontal disease severity in dentate men

have a PSA > 2.0 and > 2.5 ng/mL, and more likely to have a PSA > 4.0 ng/mL, compared to dentate men without periodontal disease.

Association between edentulism and PSA

Similar patterns were observed for edentulism. After adjusting age and race/ethnicity, the natural logarithm of PSA concentration was significantly lower in edentulous men compared to dentate men without periodontal disease (Table 2). However, after further adjusting for BMI, education, income, cigarette smoking, and diabetes status, the association was not significant.

Although the age and race/ethnicity-adjusted associations were not statistically significant, edentulous men appeared to be less likely to have elevated PSA regardless of the cut-off value, compared to dentate men without periodontal disease (Table 3). After further adjustment for BMI, education, income, cigarette smoking, and diabetes, edentulous men were less likely have to have an elevated PSA > 2.0 and > 2.5 ng/mL, and more likely to have a PSA > 4.0 ng/mL, compared to dentate men without periodontal disease; these associations were not statistically significant.

Sensitivity analysis

In sensitivity analysis, after excluding men who had received periodontal disease treatment, the association of periodontal disease and edentulism with PSA concentration did not appreciably change (Table 4). Although the associations were not significant, participants with more severe periodontal disease or edentulism were more likely to have

elevated PSA, regardless of the cut-off values of elevated PSA (Table 5). In a second sensitivity analysis, after excluding men with extreme PSA concentration (PSA > 5.35 ng/mL), results were similar to the main analysis (Table 4 and Table 5).

Discussion

In this nationally representative, cross-sectional sample of US men aged ≥ 40 years old without a prostate cancer diagnosis, periodontal disease severity and edentulism were not statistically significantly associated with total serum PSA concentration taking into account age, race/ethnicity, BMI, education, income, smoking, and diabetes.

Previous studies have investigated the association between periodontal disease and PSA. Joshi et al. reported that men with a clinical attachment level ≥ 2.7 mm and moderate/severe prostatitis had higher PSA levels than those with either condition alone [6]. The same research team also reported that periodontal disease treatment improved prostate symptom scores and reduced PSA concentration in men who underwent prostate biopsy and had chronic periodontal tissue inflammation [7]. In contrast, a prospective study suggested that periodontal disease treatment had no effect on PSA reduction [8]. Those studies were small and not conducted in the general population of men in the age range for prostate cancer screening. If periodontal disease increased PSA level, we would expect a positive association between periodontal disease and prostate cancer risk even if periodontal disease were not a cause of prostate cancer. Two large US cohort studies conducted during the era in

Table 4 Sensitivity analyses for association of periodontal disease severity and edentulism with serum prostate-specific antigen concentration, men in NHANES 2009–2010^a

	No PD	Mild	Moderate	Severe	Edentulism	<i>P</i> -trend ^d
ln(PSA) coefficients (95% CI)						
Excluding participants who ever had periodontal treatment						
No.	265	81	358	158	69	
Model 1 ^b	Reference	-0.17 (-0.35, 0.00)	-0.14 (-0.35, 0.07)	-0.15 (-0.50, 0.21)	-0.14 (-0.36, 0.09)	0.24
Model 2 ^c	Reference	-0.16 (-0.32, 0.00)	-0.13 (-0.32, 0.07)	-0.16 (-0.49, 0.18)	-0.10 (-0.37, 0.17)	0.26
Excluding men with PSA concentration above the 95 th percentile						
No.	309	101	470	221	98	
Model 1 ^b	Reference	-0.20 (-0.39, 0.00)	-0.15 (-0.27, -0.02)	-0.15 (-0.42, 0.12)	-0.24 (-0.44, -0.03)	0.07
Model 2 ^c	Reference	-0.20 (-0.37, -0.02)	-0.13 (-0.25, 0.00)	-0.14 (-0.39, 0.10)	-0.21 (-0.42, 0.01)	0.08

^aPD periodontal disease, CI confidence interval^bModel 1 adjusted for age in years (continuous) and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other)^cModel 2 adjusted for age in years (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), body mass index (continuous), annual family income (<\$25,000, \$25,000–\$74,999, >\$74,999), education (<high school, high school, >high school), smoking (never, former, current), and diabetes (non-diabetic, pre-diabetic, diabetic)^d*P* for trend for periodontal disease severity in dentate men**Table 5** Sensitivity analyses for the association of periodontal disease severity and edentulism with elevated serum prostate-specific antigen, men in NHANES 2009–2010^a

	No PD	Mild	Moderate	Severe	Edentulism	<i>P</i> -trend ^d
Odds ratio (95% CI)						
Excluding participants who ever had periodontal treatment						
PSA > 2 ng/mL	48	9	89	31	24	
Model 1 ^b	Reference	0.99 (0.37, 2.65)	1.16 (0.64, 2.13)	1.02 (0.32, 3.29)	1.07 (0.49, 2.35)	0.83
Model 2 ^c	Reference	1.01 (0.38, 2.67)	1.22 (0.63, 2.35)	0.99 (0.30, 3.28)	1.18 (0.41, 3.38)	0.80
PSA > 2.5 ng/mL	31	6	76	25	21	
Model 1 ^b	Reference	1.14 (0.30, 4.36)	1.56 (0.76, 3.17)	0.97 (0.43, 2.18)	1.13 (0.46, 2.80)	0.85
Model 2 ^c	Reference	1.16 (0.32, 4.29)	1.55 (0.71, 3.42)	0.90 (0.38, 2.14)	1.04 (0.43, 2.50)	0.84
PSA > 4.0 ng/mL	8	3	39	10	12	
Model 1 ^b	Reference	1.28 (0.10, 17.15)	2.80 (1.01, 7.74)	1.80 (0.45, 7.14)	1.97 (0.42, 9.27)	0.21
Model 2 ^c	Reference	1.35 (0.10, 17.67)	3.35 (1.13, 9.95)	2.14 (0.52, 8.73)	2.95 (0.68, 12.79)	0.06
Excluding men with PSA concentration above the 95 th percentile						
PSA > 2 ng/mL	48	9	92	38	20	
Model 1 ^b	Reference	0.79 (0.28, 2.25)	0.93 (0.49, 1.78)	0.83 (0.27, 2.58)	0.59 (0.21, 1.66)	0.47
Model 2 ^c	Reference	0.76 (0.28, 2.04)	0.93 (0.47, 1.83)	0.76 (0.25, 2.33)	0.54 (0.16, 1.87)	0.42
PSA > 2.5 ng/mL	29	5	71	27	16	
Model 1 ^b	Reference	0.81 (0.17, 3.77)	1.18 (0.48, 2.91)	0.88 (0.37, 2.11)	0.62 (0.25, 1.54)	0.56
Model 2 ^c	Reference	0.75 (0.18, 3.19)	1.10 (0.45, 2.65)	0.74 (0.34, 1.63)	0.53 (0.23, 1.13)	0.27
PSA > 4.0 ng/mL	3	2	21	8	3	
Model 1 ^b	Reference	0.66 (0.07, 6.23)	1.62 (0.32, 8.13)	1.52 (0.38, 6.09)	0.48 (0.05, 4.83)	0.95
Model 2 ^c	Reference	0.71 (0.07, 7.06)	2.29 (0.48, 10.99)	2.18 (0.46, 10.37)	0.84 (0.09, 7.68)	0.45

^aPD periodontal disease, PSA prostate-specific antigen, CI confidence interval^bModel 1 adjusted for age in years (continuous) and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other)^cModel 2 adjusted for age in years (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), body mass index (continuous), annual family income (<\$25,000, \$25,000–\$74,999, >\$74,999), education (<high school, high school, >high school), smoking (never, former, current), and diabetes (non-diabetic, pre-diabetic, diabetic)^d*P* for trend for periodontal disease severity in dentate men

which PSA-based prostate cancer screening was common reported no association between periodontal disease and prostate cancer risk [14, 15], while a large South Korean cohort study reported a modest positive association (no information was provided on whether the men in this cohort were PSA-screened) [16].

Our findings are contrary to our hypothesis that more severe periodontal disease and edentulism are associated with higher serum PSA and a greater likelihood of elevated PSA in the general population. We did note that men with mild periodontal disease tended to have lower PSA than men without periodontal disease after adjustment. While this observation could be due to chance, we cannot rule out that an influence of mild periodontitis on the inflammatory/immune status systemically, or in the prostate. Studies are not consistent in whether periodontitis produces a shift in immune profiles systemically [17, 18], and no information is available, to our knowledge, specifically in the prostate.

Strengths of this study include that we studied a US nationally representative sample of men in the age range for PSA-based prostate cancer screening, increasing the likelihood that the findings are generalizable; we used data to classify the severity of periodontal disease and edentulism from a dental examination performed as part of the NHANES protocol rather than a recalled history, reducing measurement error as compared to self-reported periodontal disease; and we used data on serum PSA concentration measured as part of the NHANES protocol not based on access to care, reducing selection bias. Moreover, we used different cut-off values for elevated PSA, allowing a thorough assessment of the association between periodontal disease and elevated PSA for clinical relevance.

Several aspects of our study warrant discussion. First of all, this study is the cross-sectional, and no temporal relationship between the periodontal disease severity and change in PSA could be established using this design. Second, we included edentulism in this study because periodontitis is the major cause of edentulism in the USA, and loss of all teeth due to periodontitis is reflective of the most severe state [15]. However, severe periodontitis is not the only cause of edentulism, and other causes such as lack of access to dental care cannot be ruled out [15]. Third, NHANES did not measure PSA in men who had a recent biopsy in past month or current infection or inflammation of the prostate. These may have been the men with the higher and/or elevated PSA, although it is unknown whether the reason for higher/elevated PSA was periodontal disease versus another reason. Fourth, PSA was measured in those without a doctor's diagnosis of prostate cancer, but we do not know whether any of these participants had undiagnosed prostate cancer. In men with prostate cancer, the greater source of PSA could be derived from the prostate cancer itself, which could reduce the ability to detect the link between periodontal disease

and non-cancer derived PSA. Fifth, we had limited statistical power to detect small associations between periodontal disease and elevated PSA. However, the null association we found is consistent with one prospective study [8]. With respect to our aim of evaluating the link between periodontal disease and elevated PSA in the context of prostate cancer screening, evidence from two prospective studies suggests that periodontal disease is not important for prostate cancer risk [14, 15].

In summary, in this US nationally representative sample of middle-aged and older men, those with periodontal disease did not have higher serum PSA after taking into account age and other factors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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