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Refining exposure definitions for studies of periodontal disease and systemic disease associations

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Abstract

Background—Substantial variation exists in reported associations between periodontal infections and cardiovascular disease. Imprecise periodontal exposure definitions are possible contributors to this variability. We studied appropriate exposure definitions for studying associations between clinical periodontal disease (PD) and systemic disease.

Methods—Data originate from men and women aged 20–79 enrolled in the Study of Health in Pomerania (SHIP) from 1997–2001. Age and sex-adjusted correlation analysis identified PD definitions with the highest cross-sectional associations with three subclinical markers of systemic disease: plasma fibrinogen (n = 3481), serum hemoglobin A1c (HbA1c) (n = 3480), and common carotid artery intima-media thickness (c-IMT) (n = 1745, age ≥ 45).

Results—In men and women, percent of sites with attachment loss (AL) ≥6 mm and tooth loss both revealed the highest correlation with HbA1c (ρ = 0.11; several other definitions related similarly), while the strongest fibrinogen correlation was observed with percent of sites with pocket depth ≥3 mm (ρ = 0.19). Findings for c-IMT among men were strongest for percent of sites with AL ≥6 mm (ρ = 0.14; several other definitions related similarly) while among women, percent of sites with pocket depth ≥5 or 6 mm had the highest observed correlation (ρ = 0.13).

Conclusions—A range of near optimal definitions varied according to gender and whether the systemic disease marker reflected an acute or chronic situation. Pocket depth was more strongly correlated with the acute marker fibrinogen while attachment and tooth loss tended to be more strongly correlated with the chronic markers, HbA1c, and c-IMT. These findings can be useful in designing future studies investigating the association between PD and systemic disease.

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Keywords

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Periodontal disease (PD) is associated with several chronic diseases, particularly cardiovascular disease (CVD), although it remains unresolved whether these associations are causal (1–5). While several prospective studies have observed an association between periodontal status and incident CVD (6–9), other studies have not found any association (10–12). For review, see (1, 13, 14). The lack of a precise epidemiologic definition for PD possibly contributed to these conflicting results.

Periodontal *disease* is characterized by the degradation of periodontal tissues as a result of underlying periodontal *infections* and inflammatory response (15). Hypotheses linking PD and CVD stem from the broader question of infection induced/inflammation mediated systemic disease (16).

To define periodontal infections, surrogate definitions have been used including self-report (6), pocket depth (7), attachment loss (AL) (17), bone loss (18, 19) and bacterial burden (20, 21). Tooth loss might also be useful in representing periodontal infections, particularly in elderly populations, where tooth loss is often a consequence of periodontal infections (22).

Appropriate definitions of PD should ideally incorporate information concerning current and/or historical infections depending on the proposed biological mechanisms linking them to outcomes. Definitions that represent current infections are likely better suited to acute, transient outcomes. Outcomes with long induction periods might require definitions that reflect historical cumulative exposure to periodontal infections. Traditionally, pocket depth represents acute infection/inflammation, while AL and/or tooth loss represent chronic infections of sufficient duration to have elicited irreversible damage.

We explored the value of various clinical definitions of PD for use in epidemiologic studies of systemic disease risk by identifying definitions having the highest cross-sectional correlations with systemic disease markers. The goal of this approach was to inform future methodological approaches to creating PD exposure definitions based on clinical periodontal measures. We therefore operated under the *assumption* that a true causal relationship exists between oral and cardiovascular health. For this purpose, we have selected three dependent variables known to be risk markers for cardiovascular disease: (1) fibrinogen, an acute-phase reactant related to inflammation and hemostatic activity, (2) hemoglobin A1c (HbA1c), a glycosylated protein that serves as a marker of intermediate-term blood glucose level, and (3) common carotid artery intima-media thickness (c-IMT), a long-term marker of atherosclerosis. These variables were selected to reflect three possible biological pathways to clinical CVD and to provide examples of acute and chronic situations.

Materials and methods

The Study of Health in Pomerania (SHIP) is a cross-sectional population-based survey in northeast Germany involving the cities of Greifswald, Stralsund and Anklam and 29

surrounding villages. The 1995 population in this catchment area was 212 157. The three cities of the region (17 076–65 977 inhabitants) and the 12 towns (1516–3044 inhabitants) were selected, and then 17 of 97 smaller towns (<1500 inhabitants) were randomly drawn. German subjects with main residency in selected areas were randomly drawn, proportional to each community population and stratified by age and gender. A representative sample of 7008 adults aged 20–79 years was invited to participate. This two-stage cluster sampling method was adopted from the World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease Project, Augsburg Germany (23) and yielded 12 balanced 5-year age strata (20–79 years) for both sexes. After deleting 746 individuals (126 died; 615 moved away; 5 had severe medical problems) from the sample, 6262 were invited. The final sample, $n = 4310$, reflects a participation rate of 68.8% (24).

Presently, subjects were excluded as follows: 15 refused the whole dental exam; 499 were edentulous; 16 had no teeth in the quadrants measured; 37 could not receive a periodontal exam for various reasons (i.e., refusal, medical indications); 186 did not receive AL measurements because of crowns. After these exclusions, yielding $n = 3557$ participants with clinical periodontal data, we created three separate subgroups corresponding to participants with complete data collected for fibrinogen ($n = 3481$), HbA1c ($n = 3480$) or c-IMT ($n = 1745$, limited to ages ≥45 years). Data collection carried out between October 1997 and May 2001 after obtaining written consent from participants. The University of Greifswald's, Institutional Review Board approved the study.

Dental examination

Tooth count (including 3rd molars) and location were assessed. The periodontal probe PCP 11 (Hufriedy, Chicago, IL, USA) assessed probing depth (PPD) and clinical AL for all examined teeth (except 3rd molars) at four sites/tooth (mesiobuccal, midbuccal, distobuccal, midlingual) using the half-mouth method on the right or left-side in alternate subjects. The occurrence of bleeding on probing (BOP) was evaluated on the 1st molar, the canine, and the central incisor (up to 24 sites/mouth). When teeth were missing, the next distal tooth was evaluated.

Calibrated examiners performed the examination. Annual calibration exercises were performed on non-enrolled subjects yielding an intraclass correlation of 0.82–0.91 per examiner and an interrater correlation of 0.84 (25).

Fibrinogen and HbA1c assessment

Plasma fibrinogen concentrations were assayed according to Clauss using an Electra 1600 analyzer (Instrumentation Laboratory, Barcelona, Spain). The laboratory % CV is 2.8% for mean values of 2.5 g/l (range 2.1–2.9 g/l); and 7.3% for mean values of 1.0 g/l (range 0.6–1.4 g/l). Hemoglobin A1c was measured by HPLC (ClinRep HbA1C, Recipe Chemicals + Instruments GmbH, Munich, Germany) with a % CV of 1.5%.

Ultrasound examination

Certified examiners scanned the extracranial carotid arteries bilaterally with B-mode ultrasound using a 5 MHz linear probe array transducer and a high-resolution instrument

(DIASONICS VST Gateway) with the participant in horizontal position. Scans from the distal straight portion (1 cm in length) of both common carotid arteries were recorded. The mean far-wall c-IMT was calculated by averaging the 10 consecutive measurements (in 1 mm steps) from the bulb bilaterally, by trained and certified readers. c-IMT reproducibility was assessed on 25 duplicate scans as previously described (26). Briefly, Spearman correlation coefficients for intraobserver and intrareader measurements were >0.95 and the mean differences (±2 SD) were <1% (±10%). Between-observer and between-reader correlations were >0.90 with mean differences (±2 SD) <5% (±15%).

Periodontal disease definitions

Candidate PD definitions were defined at the patient level according to the extent and severity of clinical PD, both in its acute (PPD and BOP) and chronic (AL and tooth loss) forms. The terms ‘extent’ and ‘severity’ are adapted from the method reported by Carlos et al. in defining the extent and severity index (27).

For both PPD and AL, candidate definitions were defined for extent of PD beyond severity thresholds ranging from 3–10 mm, as follows: (1) number of sites ≥ a given severity threshold (a measure of absolute burden giving equal weight to all sites ≥ specified severity); (2) percent of sites ≥ a given severity threshold, calculated within each mouth by dividing the number of sites ≥ a given severity threshold by total number of sites measured; (3) sum of mm ≥ a given severity threshold (absolute burden, weighting deeper pockets more heavily than shallower pockets), (4) mean of mm ≥ a given severity threshold (proportionate burden, weighting deeper pockets more heavily than shallower pockets).

Alternatively, 16 dichotomous threshold definitions were created based on the existence of any sites with PPD or AL ≥ a given severity threshold (i.e., participants were defined yes/no to having any PPD ≥ 3 mm etc). Finally, the number and percent of measured sites with BOP; number of missing teeth (including 3rd molars); and overall mean PPD and AL were considered.

Statistical analysis

Analyses were performed in PC-SAS Windows 8.0 or R Windows 2.2.1. Partial (age, sex) correlations were performed at the patient level between each candidate periodontal variables and each of the dependent variables fibrinogen, HbA1c and c-IMT. Statistical significance of differences in correlation between candidate periodontal variables within each dependent variable was tested using the ‘compOverlapCorr’ package in R (Li and Zhu 2006; see R user’s manual). This is based on a method for comparing correlated correlations between variables (γ,$X1$) and (γ,$X2$), described by Meng et al. (28). The correlations are correlated through a shared dependent variable, γ, and correlation between $X1$ and $X2$. The algebraic formula for the Z-test for the significance of the difference between two sample correlation coefficients (i.e., $\rho_{\gamma,X1}$ and $\rho_{\gamma,X2}$), is as follows: ($z_{r1}-z_{r2}$)*square root of ((N–3)/2(1−r_x)/h)), where N = sample size; z_{ri} is the Fisher z-transformed (a) $r_{\gamma Xi}$; r_x is the correlation between the two predictor variables $X1$ and $X2$; $r^2_{1,2\text{mean}} = (r^2_{\gamma,X1} + r^2_{\gamma,X2})/2$, $h = 1 - f(r^2_{1,2\text{mean}})/(1 - r^2_{1,2\text{mean}})$; $f = (1 - r_x)/(2(1 - r^2_{1,2\text{mean}}))$ which was required to be ≤1. This formulation shows that statistical significance of differences between two correlation

coefficients $\rho_{Y,X1}$ and $\rho_{Y,X2}$ depends strongly on the sample size and correlation between the two candidate periodontal definitions $\rho_{X1,X2}$, which ranged from 0.52–0.92 in these data. For periodontal measures with relatively low correlations with each other ($\rho = 0.52$) a difference in $\rho_{Y,X1}$ and $\rho_{Y,X2}$ of 0.042 for $n = 3480$ or 0.06 for $n = 1745$ would be needed to declare $P < 0.01$ (conservatively selected because of multiple comparisons). For periodontal measures more highly correlated ($\rho = 0.92$), differences between $\rho_{Y,X1}$ and $\rho_{Y,X2}$ of 0.017 for $n = 3480$ or 0.024 (for $n = 1745$) would have $P < 0.01$.

To illustrate the strength of association and risk assessment, odds ratios for elevated systemic disease risk markers, as well as their adjusted means are presented across increasing quintiles of selected periodontal definitions. For this purpose, we selected the periodontal definitions demonstrating the strongest observed correlations with each systemic marker in the aforementioned correlation analysis. This approach also assessed goodness-of-fit of the linear model implied in the correlation analysis. Supplementary analyses were performed using natural logarithm transformed values of all outcome variables to reduce the influence of outliers; no meaningful differences were noted. Tooth loss results are based on a maximum of 32 teeth and were unchanged when excluding 3rd molars from tooth count.

Results

Mean (SD) participant age in the baseline SHIP evaluation was 47 (15) years and 50% were women who were on average 2 years younger than men (46 versus 48 years, $P < 0.005$). After age adjustment, mean fibrinogen, HbA1c, and c-IMT values were 2.9(0.7) mg/dl, 5.5(0.9)%, and 0.81(0.16) mm among men and 3.0(0.7) mg/dl, 5.3(0.7)% 0.74(0.15) mm among women, respectively. All gender comparisons were statistically significantly different ($P < 0.0001$).

On average, women had slightly fewer teeth than men after age adjustment (21.6 versus 22.3 teeth respectively; $P < 0.001$) and had marginally fewer measured periodontal sites 40.8 versus 41.4 sites ($P = 0.09$). Despite more tooth loss among women, men had higher levels of PD. Age-adjusted mean PPD among men and women was 2.6 versus 2.4 ($P < 0.0001$); mean AL values were 2.9 mm versus 2.4 mm in men and women respectively ($P < 0.0001$). 36% of measured sites bled on probing and there were no gender differences. These trends were consistent across all candidate definitions of PD. Population distributions for PPD and AL candidate definitions are shown in Table 1. Participants had few greatly affected sites, e.g., < 9% of participants had 1 or more site/mouth with AL ≥ 10 mm.

After sex adjustment, age was highly correlated with PD and tooth loss. The highest correlation with age, $\rho = 0.68$, occurred for the percent of sites with AL ≥ 3 mm. The sex-adjusted correlations of age with fibrinogen, HbA1c or c-IMT were $\rho = 0.25$, $\rho = 0.35$ or $\rho = 0.43$, respectively.

In age and sex-adjusted analyses, fibrinogen was maximally correlated with percent of sites with PPD ≥ 3 mm ($\rho = 0.19$) which was highly statistically significantly different than the next closest correlation of $\rho = 0.15$ for mean PPD ($P < 0.0001$). Results were consistent in

gender subgroups, although correlations between any given periodontal definition and fibrinogen tended to be stronger among men (Table 2).

HbA1c showed weak age and sex-adjusted correlations with clinical periodontal measures and no clear peak correlation. Nevertheless, the difference between the highest correlation of 0.11 (% AL ≥ 6 mm) and the correlation of 0.10 for % AL ≥ 5 mm had $P = 0.02$, but the differences comparing correlations for % AL ≥ 6 mm to % AL ≥ 7, % AL ≥ 8 mm or number of teeth (ρ~0.10–0.11) had $P > 0.05$. As described in the methods, these differential P-values – despite nearly identical correlation coefficients – resulted from the high correlation ($\rho = 0.92$) between % AL ≥ 6 mm and % AL ≥ 5 mm. Gender-specific trends (Table 2) were consistent with these pooled findings, although power to detect statistically significant differences is diminished in the subgroup analyses.

Age and sex-adjusted results for c-IMT were similar to the aforementioned HbA1c results in the pooled sample. However, gender-specific findings show that the strongest correlations between PD and c-IMT among men occurred for % AL ≥ 5 mm ($\rho = 0.14$), while among women, the strongest correlation was % PPD ≥ 5 mm or % PPD ≥ 6 mm ($\rho = 0.13$ for either).

To further illustrate the nature of the relationships described above, Table 3 provides gender-specific mean fibrinogen, HbA1c, and c-IMT values across quintiles of periodontal definitions. There was a graded increase in fibrinogen, HbA1c, and c-IMT across quintiles of PD. The strongest increase was observed for fibrinogen which increased by 62% (relative to the gender-specific standard deviation of fibrinogen) in men and 49% in women across quintiles of PD. HbA1c and c-IMT increased by approximately 30% and 25%, respectively, with trends being slightly stronger among men, but statistically significant in both genders. A threshold relation is visually suggested for both genders, in which most of the increases in HbA1c and c-IMT occur in either the fourth or fifth quintile. The differences in levels of mean fibrinogen, HbA1c, and c-IMT between quintiles 1 and 5 were consistently greater than any differences observed between levels of dichotomous periodontal variables – for example, between participants with and without any PPD ≥ 8 mm (data not shown).

In logistic regression analyses (Table 4) associations between PD and dichotomous systemic disease markers remain evident. For brevity, only results for the periodontal definitions demonstrating the strongest correlations from Table 2 are presented in Table 4. Nevertheless, results from logistic regression sensitivity analyses (data not shown) supported the correlation trends presented in Table 2.

Correlations of the systemic markers with PD definitions based on BOP, means and sums ≥ various severity thresholds, or on the presence of at least one severe site, were similar or less informative than results in Table 2 (data not shown).

Discussion

Studies in this population (17, 29, 30) and others (7, 31–35) have consistently shown moderate positive associations between PD and markers of systemic disease (20, 36), after extensive multivariable adjustment for potential confounders. To what degree the strength of

these relationships depends on exposure definitions has received little study. We examined this issue with a side-by-side comparison of multiple clinical PD definitions to find those that most closely relate cross-sectionally to three markers of systemic disease chosen *a priori*. Definitions were based on both current and historical infection information (PPD, BOP or AL), extent of mouth involvement (number versus percent of "diseased" sites), and severity of disease (mm of PPD or AL beyond various thresholds). Regarding historical periodontal infections, an important consideration is the site level selection bias induced by tooth loss because the most severely diseased teeth have a lower probability of remaining for clinical examination in epidemiological studies. Moreover, Splieth et al. reported that teeth are extracted at an early stage of PD in this German population (37). Therefore, we included tooth loss as a candidate PD definition since it might represent the longest history, and greatest severity of periodontal infections in this population (17).

In this study of 20–79 year old East German men and women, the candidate definition of PD that demonstrated the highest correlation with respective dependent variables varied according to the systemic disease marker studied. The strongest correlates of fibrinogen were relative measures of PPD utilizing low severity thresholds (i.e., % PPD ≥ 3 mm). Regarding HbA1c, correlations were robust across various definitions, although tooth loss and relative measures of AL or PPD utilizing intermediate severity thresholds tended toward higher correlations. Results for c-IMT were similar to those for HbA1c, although among men % AL measures tended to be much stronger correlates of systemic disease markers than % PPD measures, while the converse was true among women. Number of teeth was only correlated with c-IMT among men but not women. Correlations consistently waned with severity thresholds >6 mm. Various means, sums, and functions of number rather than percent of sites, as well as dichotomized periodontal definitions based on the presence/absence of any site with severe PPD or AL (i.e., any PPD ≥ 8 mm) were consistently less informative than definitions that utilized percent of sites.

Beck et al. (38) have shown that BOP and PPD – markers of current infection – demonstrated the strongest relationship with soluble-intercellular adhesion molecule (sICAM) and high sensitivity C-reactive protein (hs-CRP). The authors suggest that this might be expected since hs-CRP (like fibrinogen) is an acute phase reactant and sICAM is a relatively short-lived marker of vascular stress. Therefore, these markers should correlate better with current infections as opposed to historical infections. Our finding that PPD definitions utilizing low severity thresholds yielded the strongest correlation with the acute phase reactant fibrinogen supports this notion.

It is plausible that short-term infections can alter systemic biomarkers, while the infections must be maintained to have an appreciable impact on chronic systemic diseases. This maintenance is manifested through chronic measures of PD, specifically, increased AL or tooth loss (39). Accordingly, HbA1c (representing several months' glucose levels) and c-IMT (indicating accumulated atherosclerotic damage) are later stage manifestations of their respective disease processes and tended to have the highest correlations with AL and tooth loss in these data.

The fact that periodontal definitions demonstrating the strongest correlations with c-IMT differed by gender is of interest. Previous reports (18), besides our own from the SHIP population (17, 30), have suggested gender differentials between PD and systemic disease. Among reasons for these gender differences, the data reported here suggest that different meanings of various periodontal measures in men and women might play a role. For example, as previously suggested (17), the attributable risk of osteoporosis for tooth loss and AL (40) might be higher among women than men, making tooth loss and AL less precise measures of historical infectious exposure among women. This finding also highlights the potential usefulness of sensitivity analyses in studies reporting on associations between clinical PD and systemic disease because there are no standardized definitions of PD when considered as exposures for systemic disease risk.

Our finding that definitions incorporating sites with mild-to-moderate PPD and AL correlate best with systemic disease markers might appear to be at odds with the intuitive picture of the association between PD and systemic disease previously offered by Offenbacher et al. They point out that in subjects with *advanced periodontal disease*, the cumulative area of inflamed periodontal pockets compromise an area roughly equivalent to the ventral forearm surface (41). Accordingly, most researchers with a periodontal background have reasonably considered advanced PD with deep pockets or advanced AL as the sine qua non of *exposure* to periodontal infections. However, data from several populations have shown that PD is characterized with only a few sites of advanced periodontal breakdown (42–44) while the majority of sites have modest AL and little pocketing. In the context of etiologic exposures for systemic disease, the host immune response in the earliest stages of periodontal infections might have important systemic effects.

This translates into a subclinical disease framework which has not been traditionally embraced by dental clinicians, where ‘healthy’ periodontal sites not only have the potential to develop PD but where subclinical pathological processes might be ongoing in these sites and have systemic effects. This is supported by data from patients with treated PD. Van der Velden et al. showed in an experimental gingivitis model (45) that periodontally diseased subjects with successful treatment, developed higher levels of gingival bleeding than subjects without a PD history. Albandar et al. (46) observed that sites with PPD ≤ 3 mm in subjects with aggressive periodontitis have a higher volume of crevicular fluid and contain higher inflammatory activity than sites ≤3 mm in healthy control subjects. Trombelli et al. confirmed this by showing that individuals with successfully treated aggressive periodontitis have a higher crevicular fluid volume than healthy subjects (47, 48). Population-based data from INVEST, found substantial levels of the four species *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Treponema denticola and Tannerella forsythia* in shallow pockets, which increased the risk of BOP in these sites (16).

Although the notion of subclinical PD has struggled to gain traction in periodontology, in the context of systemic disease studies, assessment of subclinical PD might be as important as clinical disease. A periodontium with limited signs of periodontitis could still contain sufficient infectious and inflammatory exposure to cross the threshold necessary for a systemic response. If PD definitions fail to correctly identify individuals with *relevant* biological exposure, there is high potential for exposure misclassification. In most situations,

this would result in estimates of exposure-disease associations that were biased toward the null.

The use of half-mouth periodontal exams might be a limitation in this study, since others have shown them to underestimate the prevalence of PD (49). However, previous studies have shown that relative definitions of PD (i.e., % of sites ≥ severity thresholds) do not meaningfully underestimate disease in half-mouth protocols, which minimizes the potential for bias in relation to our observed trends for relative periodontal definitions (27). Although every effort was made to standardize periodontal measurements and our systemic disease markers, we cannot unequivocally exclude the potential influence of differential measurement error. The use of correlation analysis assumes a linear association between PD and our systemic outcomes. Although the associations presented might not be perfectly linear, and in some cases exhibit patterns consistent with a threshold effect, we observed no major violations of the linearity assumption. We believe the correlation analysis is robust enough to identify meaningful trends in the exposure disease associations we have presented, while also providing a unique method to test whether these trends are likely to have occurred by chance. Finally, these cross-sectional data preclude any comment regarding definitions most predictive of incident systemic disease risk.

Nevertheless, we report that: (1) severity threshold was an important factor influencing correlations between PD definitions and systemic disease markers; (2) optimal periodontal definitions varied by gender and according to whether the systemic disease marker reflected an acute or chronic situation; (3) relative definitions of PD performed better than absolute measures.

It is advisable for future studies assessing PD as a risk factor for systemic disease to include, at minimum, findings for a range of relative periodontal definitions. By doing so, results will be more readily comparable across studies and amenable to efficient systematic reviews and meta-analyses. We believe these methodological findings are useful in designing future studies investigating the association between PD and systemic disease.

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Table 1

Mean and standard deviations of periodontal disease according to selected candidate definitions that employ either attachment loss (AL) or pocket depth combined with eight severity thresholds and two methods of summarizing extent of disease

	Attachment loss (mean ± SD)				Pocket depth (mean ± SD)			
Severity threshold (mm)	Number of sites ≥ severity thresholds	Percent of sites ≥ severity thresholds (%)	Sum of mm ≥ severity thresholds	Mean mm ≥ severity thresholds	Number of sites ≥ severity thresholds	Percent of sites ≥ severity thresholds (%)	Sum of mm ≥ severity thresholds	Mean mm ≥ severity thresholds
3	13 ± 11	46 ± 35	16 ± 24	0.7 ± 1	17 ± 10	45 ± 24	7 ± 12	0.2 ± 0.4
4	7 ± 8	28 ± 32	9 ± 17	0.5 ± 0.9	4 ± 5	12 ± 17	3 ± 8	0.1 ± 0.3
5	4 ± 6	18 ± 27	5 ± 12	0.3 ± 0.7	2 ± 3	6 ± 12	1 ± 5	0.05 ± 0.2
6	2 ± 4	12 ± 22	3 ± 8	0.2 ± 0.5	1 ± 2	3 ± 9	0.6 ± 3	0.02 ± 0.1
7	1 ± 3	7 ± 17	1 ± 5	0.09 ± 0.4	0.3 ± 1	1 ± 5	0.3 ± 2	0.01 ± 0.07
8	0.7 ± 2	4 ± 13	0.8 ± 3.3	0.05 ± 0.3	0.2 ± 0.7	0.6 ± 3	0.1 ± 0.9	0 ± 0.03
9	0.3 ± 1	2 ± 8	0.4 ± 2.2	0.03 ± 0.2	0.05 ± 0.34	0.2 ± 1.6	0.06 ± 0.6	0 ± 0.03
10	0.2 ± 1	1 ± 7	0.2 ± 1.5	0.02 ± 0.1	0.03 ± 0.24	0.1 ± 1.3	0.03 ± 0.4	0 ± 0.02

Study of Health in Pomerania, 1997, n = 3557 men and women aged 20–79 years.

Table 2

Gender-specific correlations between various clinical periodontal disease (PD) definitions and selected dependent variables marking systemic disease

Exposure definition[a]	Fibrinogen men (*n* = 1698)	Fibrinogen women (*n* = 1783)	HbA1c men (*n* = 1696)	HbA1c women (*n* = 1784)	c-IMT men (*n* = 879)	c-IMT women (*n* = 866)
% AL ≥ 3	0.17(A)	0.11(B)	0.12(A)	0.05(A)	0.08(A)	0.00(B)
% AL ≥ 4	0.16(B)	0.11(B)	0.11(A)	0.07(A)	0.10(A)	0.03(B)
% AL ≥ 5	0.15(B)	0.10(B)	0.12(A)	0.08(A)	0.11(B)	0.04(B)
% AL ≥ 6	0.12(B)	0.10(B)	**0.13(A)**	0.09(A)	**0.14(A)**	0.07(A)
% AL ≥ 7	0.09(B)	0.07(B)	0.13(A)	0.06(A)	0.13(A)	0.06(B)
% AL ≥ 8	0.06(B)	0.07(B)	0.11(A)	0.08(A)	0.10(B)	0.08(A)
% AL ≥ 9	0.02(B)	0.07(B)	0.05(B)	0.08(A)	0.06(B)	0.07(B)
% AL ≥ 10	0.00(B)	0.05(B)	0.02(B)	0.09(A)	0.03(B)	0.03(B)
Mean AL[b]	0.14(B)	0.11(B)	0.13(A)	0.07(A)	0.11(B)	0.04(B)
% PPD ≥ 3	**0.21(A)**	**0.16(A)**	0.07(A)	0.01(B)	0.08(A)	0.05(B)
% PPD ≥ 4	0.13(B)	0.10(B)	0.10(A)	0.08(A)	0.08(B)	0.12(A)
% PPD ≥ 5	0.08(B)	0.08(B)	0.07(A)	0.09(A)	0.09(A)	0.13(A)
% PPD ≥ 6	0.04(B)	0.07(B)	0.07(B)	0.07(A)	0.09(A)	**0.13(A)**
% PPD ≥ 7	0.00(B)	0.05(B)	0.06(B)	0.07(A)	0.05(B)	0.06(B)
% PPD ≥ 8	0.00(B)	0.05(B)	0.04(B)	0.09(A)	0.06(B)	0.08(B)
% PPD ≥ 9	0.00(B)	0.06(B)	0.03(B)	0.08(A)	0.04(B)	0.01(B)
% PPD ≥ 10	0.00(B)	0.07(B)	0.04(B)	0.08(A)	0.06(B)	−0.02(B)
Mean PD[b]	0.16(B)	0.14(B)	0.08(A)	0.05(A)	0.09(A)	0.10(A)
Tooth count	0.10(B)	0.10(B)	0.13(A)	**0.10(A)**	0.09(A)	0.04(B)

Clinical periodontal definitions are based on percent of sites with attachment loss (AL) or probing depth (PPD) beyond selected severity thresholds ranging from 3–10 mm. Correlations are age adjusted. Study of Health in Pomerania, 1997, men and women aged 20–79 years.

[a] % of sites with AL or pocket depth (PPD) ≥ various severity thresholds (millimetres).

[b] Mean AL or pocket depth (PPD) in all measured sites.

Shaded cells represent correlations that are not statistically significantly different from zero (*P*-value > 0.01 for null hypothesis $\rho = 0$).

Bold denotes the highest observed correlation coefficient (before rounding) within each gender-specific outcome. Statistical tests of differences in correlation coefficients between the highest observed correlation and the other 18 correlation coefficients within each gender-specific outcome were performed (Ho: $\rho 1_i = \rho 2_i$); coefficients sharing a letter with the highest correlation are not statistically

significantly different ($P > 0.05$) – based on methods for comparing correlated correlation coefficients from Meng et al. (28). For example, among men, the correlation between % PPD ≥ 3 mm and fibrinogen ($\rho = 0.21$) is statistically significantly different than all other correlations between PD and fibrinogen in that column with the exception of % AL ≥3 mm.

Table 3

Mean values (±SE) of systemic disease markers across quintiles of selected periodontal disease definitions[a]

	Quintile I	Quintile II	Quintile III	Quintile IV	Quintile V	% Δ[b] QI–QV	p- for linear trend
Men							
Fibrinogen[c] (*n* = 1698)	2.70 ± 0.04	2.81 ± 0.04	2.82 ± 0.03	2.97 ± 0.04	3.14 ± 0.04	62	<0.0001
HbA1c[d] (*n* = 1696)	5.42 ± 0.03	5.43 ± 0.06	5.41 ± 0.06	5.54 ± 0.07	5.72 ± 0.07	33	0.0005
c-IMT[d] (*n* = 879)	0.80 ± 0.01	0.81 ± 0.01	0.80 ± 0.01	0.82 ± 0.01	0.84 ± 0.01	25	0.005
Women							
Fibrinogen[c] (*n* = 1783)	2.85 ± 0.04	2.92 ± 0.04	3.01 ± 0.03	2.99 ± 0.04	3.19 ± 0.04	49	<0.0001
HbA1c[d] (*n* = 1784)	5.22 ± 0.02	5.22 ± 0.05	5.30 ± 0.06	5.22 ± 0.06	5.43 ± 0.06	30	0.007
c-IMT[e] (*n* = 866)	0.73 ± 0.01	0.72 ± 0.01	0.72 ± 0.01	0.76 ± 0.01	0.77 ± 0.01	27	0.03

All values are age-adjusted. Study of Health in Pomerania, 1997, men and women aged 20–79 years.

[a] Definitions selected based on highest correlation presented in Table 2.

[b] The denominators for % Δ calculations are the respective gender-specific standard deviations for Fibrinogen (M = 0.7 g/l; W = 0.7 g/l), HbA1c (M = 0.9%; W = 0.7%) and c-IMT (M = 0.16 mm; W = 0.15 mm).

[c] Independent variable is Quintiles of % sites with pocket depth ≥3 mm.

[d] Independent variable is Quintiles of % sites with attachment loss ≥6 mm.

[e] Independent variable is Quintiles of % sites with pocket depth ≥5 mm.

Table 4

Age-adjusted odds ratios (95%CI) for elevated levels of systemic disease markers, across quintiles of selected periodontal disease definitions

	Periodontal disease Quintile II	Periodontal disease Quintile III	Periodontal disease Quintile IV	Periodontal disease Quintile V	p- for linear trend
Fibrinogen men (*n* = 1698)					
Fibrinogen 80th[a]	2.10 (1.25, 3.52)	2.08 (1.25, 3.47)	2.81 (1.71, 4.63)	4.80 (2.96, 7.80)	<0.0001
Fibrinogen 90th[a]	1.60 (0.79, 3.24)	1.70 (0.85, 3.38)	2.29 (1.18, 4.45)	4.00 (2.13, 7.54)	<0.0001
Fibrinogen women (*n* = 1783)					
Fibrinogen 80th[a]	1.13 (0.75, 1.73)	1.40 (0.93, 2.10)	1.56 (1.04, 2.34)	2.80 (1.90, 4.11)	<0.0001
Fibrinogen 90th[a]	0.94 (0.52, 1.70)	1.63 (0.96, 2.77)	1.63 (0.96, 2.78)	3.08 (1.87, 5.07)	<0.0001
HbA1c men (*n* = 1696)					
HbA1c ≥5.7%[b]	1.32 (0.92, 1.88)	1.32 (0.93, 1.88)	1.43 (1.00, 2.03)	1.70 (1.18, 2.44)	0.004
HbA1c ≥7.0%[b]	0.83 (0.33,2.07)	1.04 (0.48,2.26)	2.10 (1.08, 4.06)	2.24 (1.15, 4.36)	0.004
HbA1-c women (*n* = 1784)					
HbA1c ≥5.7%[b]	1.19 (0.77,1.85)	1.35 (0.90, 2.03)	0.97 (0.64,1.46)	1.29 (0.85, 1.96)	0.32
HbA1c ≥7.0%[b]	0.64 (0.15, 2.84)	1.16 (0.41, 3.28)	1.52 (0.61, 3.77)	3.12 (1.43, 6.82)	0.007
c-IMT men (*n* = 879)					
IMT≥80th[c]	1.07 (0.61, 1.87)	1.23 (0.73, 2.08)	1.33 (0.80, 2.20)	1.63 (1.02, 2.62)	0.03
IMT≥90th[c]	1.05 (0.42, 2.61)	2.23 (1.07, 4.64)	2.38 (1.17, 4.83)	2.45 (1.25, 4.80)	0.003
c-IMT women (*n* = 866)					
IMT≥80th[c]	0.62 (0.29, 1.35)	0.62 (0.30, 1.30)	1.41 (0.77, 2.60)	1.54 (0.80, 2.93)	0.21
IMT≥90th[c]	0.66 (0.19, 2.29)	0.60 (0.18, 2.09)	2.24 (1.00, 5.03)	2.47 (1.08, 5.67)	0.02

Study of Health in Pomerania, 1997, men and women aged 20–79 years Quintile I serves as the reference for all odds ratios.

[a] Fibrinogen outcome defined as ≥80th (3.49 mg/dl) or 90th (3.8 mg/dl) percentiles. Independent variable is Quintiles of % sites with pocket depth ≥3 mm.

[b] HbA1c outcome defined as ≥5.7% or 7.0%. 5.7% is approximately equivalent to glucose of 126 mg/dl (50). 7.0 % is often viewed as uncontrolled diabetes (51). Independent variable is Quintiles of % sites with attachment loss (AL) ≥6 mm.

[c] IMT outcome defined as ≥80th (0.89 mm) or 90th (1.0 mm) percentile.

Independent variable for IMT (men) is quintiles of % sites with AL ≥6 mm.

Independent variable for IMT (women) is quintiles of % sites with pocket depth ≥5 mm.