

Periodontal Infection, Systemic Inflammation, and Insulin Resistance

Results from the continuous National Health and Nutrition Examination Survey (NHANES) 1999–2004

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OBJECTIVE—Adverse microbial exposures might contribute to diabetogenesis. We hypothesized that clinical periodontal disease (a manifestation of microbial exposures in dysbiotic biofilms) would be related to insulin resistance among diabetes-free participants. The roles of inflammatory mediation and effect modification were also studied.

RESEARCH DESIGN AND METHODS—The continuous National Health and Nutrition Examination Survey 1999–2004 enrolled 3,616 participants (51% women) who received a periodontal examination and fasting blood draw. Participants were mean age (\pm SD) 43 ± 17 years and 28% Hispanic, 52% Caucasian, 17% African American, and 3% other. Log-transformed values of the homeostasis model assessment of insulin resistance (HOMA-IR) or $\text{HOMA-IR} \geq 3.30$ (75th percentile) were regressed across full-mouth periodontal probing depth (PD) levels using linear and logistic models. White blood cell (WBC) count and C-reactive protein (CRP) were considered as either mediators or effect modifiers in separate analyses. Risk ratios (RRs) stem from marginal predictions derived from the logistic model. Results were adjusted for multiple periodontal disease and insulin resistance risk factors.

RESULTS—In linear regression, geometric mean HOMA-IR levels increased by 1.04 for every 1-mm PD increase ($P = 0.007$). WBC mediated 6% of the association ($P < 0.05$). Among participants with $\text{WBC} \leq 6.4 \times 10^9$, PD was unrelated to $\text{HOMA-IR} \geq 3.30$. Fourth-quartile PD was associated with $\text{HOMA-IR} \geq 3.30$ among participants with $\text{WBC} > 7.9 \times 10^9$; RR 2.60 (1.36–4.97) (P for interaction = 0.05). Findings were similar among participants with $\text{CRP} > 3.0$ mg/L (P for interaction = 0.04).

CONCLUSIONS—Periodontal infection was associated with insulin resistance in a nationally representative U.S. sample of diabetes-free adults. These data support the role of inflammation as both mediator and effect modifier of the association.

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Type 2 diabetes mellitus (T2DM) is a prominent public health problem (1) currently affecting at least 17.7 million individuals in the U.S. The hallmark of T2DM is chronically elevated

fasting plasma glucose secondary to insulin resistance and impaired pancreatic β -cell function. Adverse microbial exposures, such as those observed in dysbiotic periodontal biofilms, have been suggested

as a potential risk factor for insulin resistance and T2DM development. This notion is bolstered by previous research suggesting a bidirectional relationship between periodontal disease and glycemic control among individuals with diabetes (2,3). However, research exploring periodontal infection as a diabetes risk factor among diabetes-free adults has only been initiated recently.

Two previous publications reported that the presence of periodontal disease predicted 1) a twofold increase in incident T2DM during 20 years of follow-up in a nationally representative sample of $\sim 9,000$ initially diabetes-free men and women (4); and 2) an approximately fivefold increase in the progression of A1C among 2,700 diabetes-free participants arising from a randomly selected population-based sample (5). The latter publication also reported that the infection-associated risk related to A1C progression was stronger among participants with evidence of elevated C-reactive protein (CRP) (5). These studies were unable to specifically examine the association between periodontal disease and insulin resistance.

The potential for periodontal infections to contribute to insulin resistance and overt T2DM is biologically plausible (2,6,7), and one specific causal pathway linking infections and T2DM risk is chronically elevated systemic inflammation. Systemic inflammation is known to be elevated among participants with periodontal infections and has also been shown to predict the progression of insulin resistance (8) as well as the development of T2DM (9,10).

In this study, we explored the association between clinically assessed periodontal disease (a clinical manifestation of adverse microbial exposures in dysbiotic biofilms) and insulin resistance in the continuous National Health and Nutrition Examination Survey (NHANES). We also studied whether or not there was evidence that systemic inflammation either mediated or modified the association between periodontal disease and insulin resistance.

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RESEARCH DESIGN AND

METHODS—The continuous NHANES began in 1999 and consists of six unique data sets that have been generated in 2-year cycles (i.e., 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, and 2009–2010). The survey examines a nationally representative sample of ~5,000 people each year and collects a variety of health-related data via questionnaire, physical examination, and laboratory assessments. The current analysis uses the NHANES 1999–2000, 2001–2002, and 2003–2004 cross-sections and includes $n = 3,616$ diabetes-free men and women aged 20–85 years who received a clinical periodontal examination and fasting glucose and insulin assessments. The NHANES protocol was approved by the National Center for Health Statistics institutional review board, and written informed consent was obtained from all participants.

Oral examination

The NHANES oral health examination (OHE) has been previously described (11,12). Trained dentists performed a full-mouth tooth count as well as a periodontal examination according to a random half-mouth method (excluding third molars). Periodontal probing depth (PD) and clinical attachment loss (AL) measurements were performed at two sites per tooth (mid- and mesio-facial) in the 1999–2000 cross-section (i.e., up to 28 possible sites per participant). In the 2001–2002 and 2003–2004 periodontal examinations, a third distal surface (disto-facial) measurement was added. OHE 1999–2002 used National Institute for Dental Research periodontal probes, and the 2003–2004 OHE used a technically similar Hu-Friedy PCP2 probe (12). Both instruments were color banded with PD graduations at 2, 4, 6, 8, 10, and 12 mm. When the examiner was equivocal as to the best value to assign, measurements were rounded to the next lowest band. Interexaminer reproducibility ranged from good to very good with κ scores ranging from 0.64 to 0.82 (11,12).

Fasting glucose and insulin assessments

Fasting glucose and insulin were measured at the same central laboratory. Glucose was determined according to a hexokinase enzymatic method (13) and insulin according to a radioimmunoassay (14). Glucose and insulin were used to calculate the homeostasis model

assessment of insulin resistance (HOMA-IR) as previously described (15). In brief, HOMA-IR is defined as (insulin in $\mu\text{U/mL} \times \text{glucose in mmol/L}) / 22.5$.

Risk factor assessments

A comprehensive set of questionnaires to assess risk factors relevant to both periodontal disease and insulin resistance was administered. The demographic variables age, race/ethnicity, sex, education, and poverty-to-income ratio (calculated by dividing family income by the poverty guidelines, specific to family size, as well as the appropriate year and state according to Department of Health and Human Services guidelines) were collected. Behavioral risk factor assessments included physical activity level, cigarette smoking duration and intensity, alcohol consumption, and caloric intake. Waist, weight, height, and blood pressure measurements were performed by trained research assistants according to standardized protocols. Triglycerides, total and HDL cholesterol, CRP, and white blood cell (WBC) count were measured from fasting blood samples.

Statistical analysis

Survey procedures in SAS version 9.2 and SAS-callable SUDAAN version 10 were used for all analyses.

Periodontal disease was defined according to quartiles of either mean full-mouth PD or AL values to obtain a balanced categorization of the periodontal exposure and to enable the assessment of dose responsiveness. The Centers for Disease Control and Prevention/American Academy of Periodontology (CDC/AAP) working group definition was also considered (16). The outcomes analyzed were fasting glucose, insulin, and HOMA-IR. The probability of HOMA-IR ≥ 3.30 (the population-specific 75th percentile of HOMA-IR) was regressed on quartiles of periodontal disease in logistic regression models using SAS PROC SURVEYLOGISTIC. PROC RLOGIST in SUDAAN was used to obtain multivariable-adjusted risk ratios (RRs) from fitted logistic regression models by obtaining point estimates of model-adjusted RRs as functions of average marginal predictions (17). Linear regression (SAS PROC SURVEYREG) modeled either the mean values of continuous glucose, insulin, or HOMA-IR across quartiles of periodontal disease. For insulin and HOMA-IR, both untransformed

and natural log-transformed values were considered (no meaningful differences were noted). Both arithmetic- and geometric-adjusted mean values of insulin and HOMA-IR are presented in the results. All P values presented for linear trend were based on models using a continuous periodontal exposure variable. Multivariable models were adjusted for confounding by the following variables: continuous age, poverty-to-income ratio, caloric intake, BMI, blood pressure, triglycerides, total cholesterol-to-HDL cholesterol ratio, and inflammatory biomarkers as well as race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, or other), sex, education (<high school, high-school graduate, or >high school), smoking status (never, former, or current in addition to pack-years), physical activity level in the past 30 days (none, moderate, or vigorous), and alcohol consumption (drinks/day). Mediation analyses were performed to estimate whether or not the association between periodontal infection and insulin resistance was mediated by inflammatory biomarkers (i.e., WBC or CRP) (Table 1) (18). Interactions between either WBC or CRP and periodontal infection were also examined. Categories of systemic inflammation were based on either quartiles of WBC or alternatively on CRP defined by the CDC/American Heart Association (AHA) statement on inflammatory markers in cardiovascular disease (19).

RESULTS**General characteristics**

Supplementary Table 1 presents general characteristics of study participants both weighted and unweighted to the U.S. population. Before applying NHANES weights, participants included in this analysis were aged 44 ± 17 years (age \pm SD) and 51% were women. Whites, Hispanics, and blacks represent 52, 28, and 17% of the sample (3% reported other race/ethnicity). Participants had 28 teeth on average (including third molars), and the mean PD and mean AL values were 1.2 ± 0.5 and 0.8 ± 0.9 mm, respectively. The cumulative prevalence estimates of moderate or severe periodontitis were 11 and 1%, respectively.

Higher levels of PD were associated with several demographic, SES, and lifestyle variables as summarized in Supplementary Table 1, and although many of these associations were statistically

Table 1—Inflammatory mediation of the association between periodontal infection and insulin resistance

Effect	White blood cell count					
	Estimate	SE	T value	P value	Lower 95% CL	Upper 95% CL
a (exposure→mediator)	0.21006	0.08121	2.59	0.01	0.05089	0.36923
b (mediator→outcome)	0.02894	0.00594	4.87	<0.0001	0.01730	0.04059
c (total effect)	0.09527	0.03110	3.06	0.0037	0.03431	0.15622
c' (direct effect)	0.08919	0.03090	2.88	0.0061	0.02862	0.14975
ab (mediated effect)	0.00608	0.00266	NA	<0.05	0.00087	0.01129
ab/c (WBC proportion mediated) = 6.4%						
Effect	CRP					
	Estimate	SE	T value	P value	Lower 95% CL	Upper 95% CL
a (exposure→mediator)	-0.02976	0.02881	-1.03	0.3073	-0.08624	0.02672
b (mediator→outcome)	0.01606	0.01795	0.89	0.3758	-0.01912	0.05124
c (total effect)	0.09527	0.03111	3.06	0.0037	0.03430	0.15623
c' (direct effect)	0.09574	0.03100	3.09	0.0035	0.03498	0.15651
ab (mediated effect)	-0.00048	0.00071	NA	NS	-0.00187	0.00091
ab/c (CRP proportion mediated) = -0.5%						

Men and women ($n = 3,616$) aged 20–85 years enrolled in the continuous NHANES 1999–2004. Estimates are derived from linear regression analyses modeling mean periodontal PD as the exposure, WBC or CRP as the mediator, and HOMA-IR as the outcome. a, b, c, c', and ab as described in MacKinnon (18). a is the regression coefficient summarizing the association between exposure and mediator; b is the regression coefficient summarizing the association between mediator and outcome, adjusted for exposure; c is the unadjusted regression coefficient summarizing the association between exposure and outcome (i.e., the total effect); c' is the regression coefficient summarizing the association between exposure and outcome adjusted for mediator; and ab is the cross product of a and b and represents the amount of the association between exposure and outcome that goes through the mediator.

significant in this large sample, trends across PD quartiles were generally weak in comparison with trends across quartiles of AL. Mean age varied from 44 to 45 years across PD quartiles (P for trend = 0.08), whereas mean age varied from 34 to 56 years across AL quartiles ($P < 0.01$). Similarly, mean pack-years in the first versus fourth AL quartile varied from 2 to 12, respectively ($P < 0.0001$), an increase threefold greater than observed for PD quartiles as described in Supplementary Table 1.

The arithmetic mean \pm SD fasting plasma glucose, insulin, and HOMA-IR values were 95 ± 10 mg/dL and 66 ± 48 and 2.6 ± 2.1 pmol/L. Geometric mean values of insulin and HOMA-IR were 54 and 2.1 pmol/L, respectively.

Association between periodontal disease, glucose, insulin, and insulin resistance

Values of mean fasting glucose (mg/dL) \pm SE across quartiles of mean PD were 95.3 ± 0.4 , 94.8 ± 0.4 , 95.1 ± 0.4 , and 95.3 ± 0.4 (P for trend = NS). Geometric mean values of insulin and HOMA-IR varied across PD quartiles in a dose-responsive fashion (Fig. 1). In multivariable linear regression analysis, geometric mean HOMA-IR levels increased by 1.04 for every 1 mm of mean

PD increase ($P = 0.007$), and this finding was similar when restricting the analysis to nonobese participants (regression coefficient = 1.05; $P = 0.006$).

Mean AL was not associated with glucose, insulin, or insulin resistance. Mean HOMA-IR values across quartiles of AL were 2.00 ± 0.06 , 2.03 ± 0.06 , 1.94 ± 0.06 , and 1.90 ± 0.07 (P for linear trend = 0.53); glucose and insulin data are not shown.

In fully adjusted logistic regression models, a 1-mm increase in continuous PD was associated with an increased risk of HOMA-IR ≥ 75 th percentile: RR 1.24 (95% CI 1.03–1.48); P for trend = 0.03. Findings were consistent when considering risk for HOMA-IR ≥ 75 th percentile across quartiles of PD (Table 2). Mean AL was not associated with elevated HOMA-IR risk (Table 2).

Relative to participants with no/mild periodontitis, HOMA-IR risk was not increased among participants with moderate periodontitis but was increased among participants with severe periodontitis: RRs for moderate and severe periodontitis 0.85 (0.61–1.19) and 2.30 (1.27–4.15).

Results were consistent among age-subgroups; the RRs for fourth versus first quartile of PD among participants aged 20–39 ($n = 1,732$), 40–59 ($n = 1,106$), or ≥ 60 ($n = 778$) years were 1.25 (95% CI

0.79–1.96), 1.34 (0.75–2.38), and 1.39 (0.80–2.42). Similarly, findings were consistent among nonobese participants as well as never smokers; the respective RRs comparing participants in the fourth versus first PD quartile were 1.21 (0.77–2.31) (among nonobese participants) and 1.32 (0.88–1.99) (among never smokers).

Inflammatory mediation

In linear regression analyses, there was evidence that the association between PD and HOMA-IR was mediated by WBC. Mean PD was positively associated with both WBC and HOMA-IR. Further, WBC was positively associated with HOMA-IR after adjustment for PD (Table 1). It was estimated that 6% of the total association between mean PD and HOMA-IR was mediated by WBC ($P < 0.05$) (Table 1). There was no evidence that CRP mediated the association between mean PD and HOMA-IR (Table 1).

Inflammatory interaction (effect modification)

PD was only associated with HOMA-IR in the presence of elevated systemic inflammation. For example, participants with both fourth-quartile PD and WBC values (vs. first-quartile PD and WBC) realized a 160% increase in the risk of HOMA-IR ≥ 75 th percentile: RR 2.60 (95%

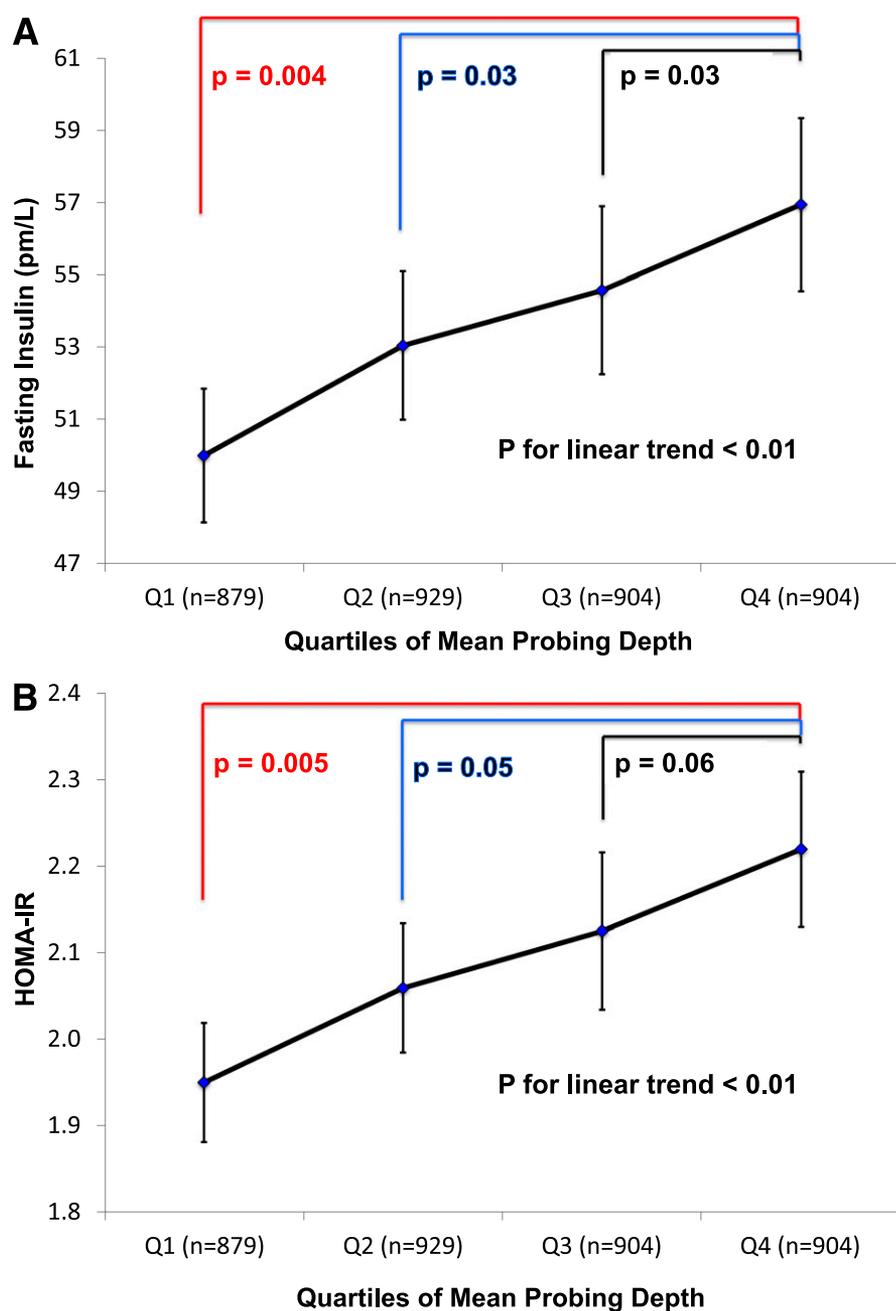


Figure 1—The association between PD quartiles and geometric mean insulin (A) and geometric mean HOMA-IR (B) values. Adjusted for age, sex, race/ethnicity, education level, smoking status, activity level, BMI, total caloric intake, systolic blood pressure, total cholesterol-to-HDL cholesterol ratio, and triglycerides. Men and women (n = 3,616) 20–85 years of age enrolled in the continuous NHANES 1999–2004. (A high-quality color representation of this figure is available in the online issue.)

CI 1.36–4.97); P for interaction = 0.05 (Fig. 2). Similarly, the RR comparing participants with fourth-quartile PD and CRP >3.0 mg/L versus first-quartile PD and CRP <1.0 mg/L was 2.22 (1.34–3.68); P for interaction = 0.04 (Fig. 2). These findings are generalizable to a sizable proportion of U.S. adults; after applying NHANES sampling weights, 16% of participants had

both mean PD values ≥50th percentile and a CRP value >3.0 mg/L, corresponding to 20,519,829 diabetes-free adults. Similarly, 24% (31,278,079) of U.S. adults had both PD ≥50th and WBC ≥50th percentile.

CONCLUSIONS—We have found periodontal PD, but not AL, to be positively

associated with increased risk of elevated fasting insulin and insulin resistance in a dose-responsive fashion. In the full sample, the risk of elevated HOMA-IR increased by ~30% across PD quartiles. There was only weak evidence for mediation by systemic inflammation but much stronger support for the hypothesis of a synergistic interaction between elevated systemic inflammation and periodontal status, such that periodontal status was only associated with insulin resistance among participants with WBC ≥6.5 × 10⁹ cells/L or CRP ≥1.0 mg/L. All findings remained after comprehensive adjustment for demographics, health-related behaviors, systemic inflammation, smoking status, and adiposity.

The current data support recently published findings that periodontal infection might be a risk factor for the development of T2DM. Previously published prospective data from the Study of Health in Pomerania (SHIP) demonstrated that baseline periodontal status predicted 5-year progression of A1C (5). These SHIP data extended a previous cross-sectional report of elevated A1C levels among participants with periodontitis (20) as well as an earlier publication from NHANES I reporting increased levels of baseline periodontal disease to predict incident diabetes during two decades of follow-up (4). Although a recent study had equivocal findings for incident diabetes in a Japanese population (21), the mean follow-up time was only 6 years, which limited the number of incident cases and minimized power to detect the association observed. Collectively, these earlier studies were limited by an inability to address the potential role of insulin resistance as a mechanistic explanation of the aforementioned A1C change and incident diabetes findings.

Chronic inflammation is a plausible biological mechanism linking infections and insulin resistance. Animal models have shown that inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), can induce a state of insulin resistance (22), possibly as a consequence of TNF-α's ability to interrupt serine phosphorylation of insulin receptor substrate-1 (23), and epidemiological data in humans have repeatedly shown inflammation to be an independent risk factor for both insulin resistance (8) and T2DM (9,10,24). There are many potential exogenous inflammatory stimuli that might trigger inflammatory responses, some of which also

Table 2—Cumulative prevalence RRs (95% CI) for HOMA-IR \geq 75th percentile by mean periodontal PD and AL categories

Model	Periodontal disease Q1	Periodontal disease Q2	Periodontal disease Q3	Periodontal disease Q4	P for trend**
	Quartiles of mean PD				
	19% (166/879)*	23% (212/929)*	26% (238/904)*	28% (254/904)*	
1	Ref	1.21 (0.95–1.54)	1.40 (1.05–1.88)	1.56 (1.18–2.07)	0.002
2	Ref	1.10 (0.84–1.44)	1.22 (0.89–1.68)	1.34 (0.98–1.83)	0.02
2b	Ref	1.03 (0.77–1.38)	1.26 (0.92–1.73)	1.38 (0.98–1.92)	0.02
3	Ref	1.00 (0.77–1.30)	1.12 (0.82–1.53)	1.26 (0.94–1.68)	0.03
4	Ref	1.00 (0.77–1.30)	1.10 (0.81–1.51)	1.24 (0.92–1.65)	0.05
	Quartiles of mean AL				
	21% (200/935)*	26% (257/974)*	25% (243/961)*	27% (255/953)*	
1	Ref	1.24 (1.00–1.55)	1.25 (0.95–1.64)	1.25 (0.99–1.59)	0.10
2	Ref	1.17 (0.89–1.54)	1.20 (0.86–1.67)	1.09 (0.77–1.54)	0.51
2b	Ref	1.16 (0.90–1.49)	1.28 (0.90–1.82)	1.20 (0.84–1.72)	0.28
3	Ref	1.11 (0.84–1.46)	1.19 (0.84–1.68)	1.05 (0.74–1.49)	0.73
4	Ref	1.10 (0.84–1.44)	1.20 (0.85–1.69)	1.03 (0.73–1.45)	0.91

Men and women ($n = 3,616$) aged 20–85 years enrolled in the continuous NHANES 1999–2004. Model 1, crude; model 2, age, sex, race/ethnicity, education level, smoking status, physical activity level, total energy intake, and BMI; model 2b, model 2 + poverty income ratio and pack-years of smoking ($n = 478$ missing poverty and pack-years data); model 3, model 2 + systolic blood pressure, total cholesterol-to-HDL cholesterol ratio, and triglycerides; model 4, model 3 + WBC and high-sensitivity CRP. *Crude cumulative prevalence of HOMA-IR \geq 75th percentile. **P for linear trend derived from models using the continuous mean PD or AL variables.

have been linked to insulin resistance and diabetes development, such as air pollution (25) and organic pollutants (26). Accordingly, periodontal infection has been repeatedly demonstrated to be associated with elevated levels of systemic inflammation (27), and periodontal therapy has been shown to result in changes in systemic monocytic gene expression (28) as well as decreases in systemic inflammation (29,30) and insulin resistance (31). Therefore, it is plausible that insulin resistance might be reduced via appropriate anti-infective/anti-inflammatory periodontal therapy.

Despite strong biological plausibility, our current findings provide only weak support for inflammatory mediation. This might be due to the fact that our inflammatory construct was limited in this analysis and importantly did not include TNF- α , which likely mischaracterizes any true causal inflammatory intermediates. Alternatively, these data do strongly support the possibility of synergy between periodontal infection and systemic inflammation, and this is unlikely to be a chance finding, as the results are statistically significant and based on a priori hypotheses generated from previously published data (5). Although the biological mechanisms that might underpin the observed interaction are not immediately obvious, it is possible that our crude

inflammatory markers (WBC and CRP) are simply surrogates of an underlying genetic susceptibility to infection-induced insulin resistance. Unfortunately, more advanced methods that could address both mediation and interaction concurrently (i.e., exposure-mediator interactions) in a complex sampling design such as NHANES are not readily available. Nevertheless, as these data are cross-sectional, results from such analyses are unlikely to add meaningful value from the standpoint of causal inference. Longitudinal studies that can more precisely investigate the interplay between microbial exposures, inflammatory response, and insulin resistance are necessary.

The fact that PD, and not AL, was associated with HOMA-IR is notable because it suggests that clinical indicators of current infection and/or inflammation are more relevant when studying cross-sectional associations between periodontal infection and insulin resistance. As previously discussed, evidence of irreversible, historical oral infection (e.g., AL) might be more informative when studying insidious and/or irreversible outcomes presumed to be partly caused by chronic infectious exposure. Alternatively, ephemeral measures, such as PD, which are closely associated with the presence of current periodontal inflammation in response to potentially

pathogenic periodontal microbiota (32,33), might be more precise for outcomes that are acute and/or reversible (34). The strong association between severe periodontitis (defined according to recommendations from the CDC/AAP working group) (16) and insulin resistance is consistent with this line of thinking because it not only requires clinical evidence of historical infection (i.e., periodontal sites with high AL) but the definition also incorporates a measure of current disease (i.e., periodontal sites with deep PD). In contrast, moderate periodontitis, which does not require clinical signs of current disease, was unrelated to insulin resistance. The low prevalence of severe periodontitis in these data precluded exploration of inflammatory interactions.

The specificity of insulin resistance findings to PD measures (as opposed to AL) is also notable because it minimizes potential confounding. Factors such as age and smoking are generally stronger risk factors for AL and radiographic bone loss but weaker risk factors for PD (35), and the current data support this notion (see RESULTS). Nevertheless, in these data, even crude associations between AL and insulin resistance were weak and not dose responsive.

The finding that increased levels of periodontal disease are associated with

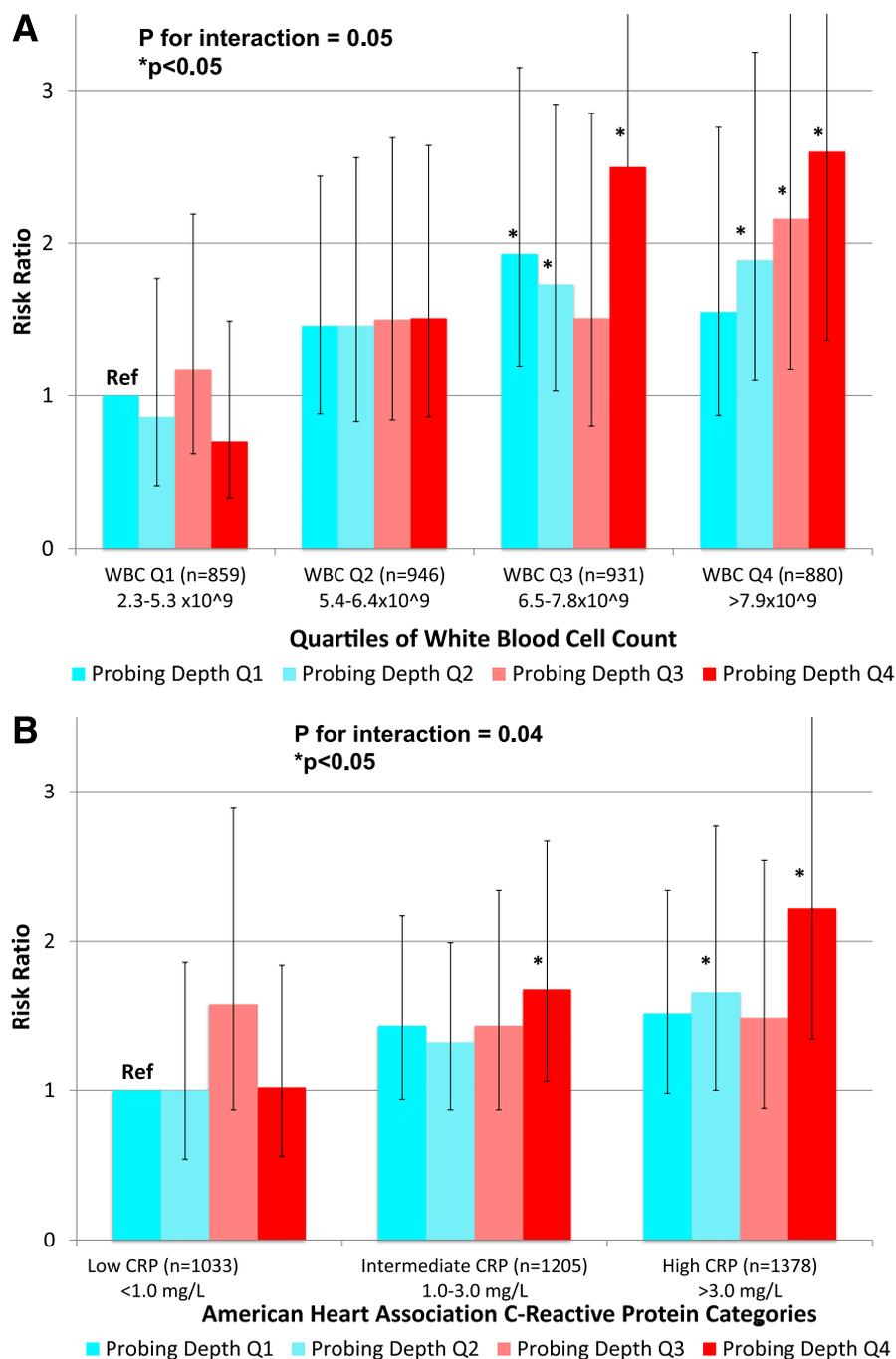


Figure 2—Cumulative prevalence RRs (95% CI) for HOMA-IR \geq 75th percentile across increasing levels of periodontal PD and either WBC count defined in quartiles (A) or CRP defined via AHA categories (B) (19). Adjusted for age, sex, race/ethnicity, education level, smoking status, activity level, BMI, systolic blood pressure, total cholesterol-to-HDL cholesterol ratio, and triglycerides. Men and women (n = 3,616) aged 20–85 years enrolled in the continuous NHANES 1999–2000.

increased fasting insulin resistance is meaningful for the prediction of future T2DM development. Elevations in insulin resistance have been repeatedly shown to be strong predictors of incident diabetes (36,37), and the HOMA-IR method has been validated for large

epidemiological studies for subjects of various ethnicities and a wide range of glucose tolerance (38).

Our exposure was based on clinically assessed measures of periodontal disease because these measures are manifestations of host response to adverse

microbial exposures in dysbiotic periodontal biofilms. Previous studies have included direct assessments of oral (39) or gut (40) microbial exposures to study either cardiovascular or obesity risk; similar approaches can provide more precise characterizations of infection–insulin resistance associations in future studies. Consequently, our current findings may be attenuated due to a lack of comprehensive information on microbial exposures, both oral and otherwise. The fact that these data are cross-sectional is also a limitation, as we cannot infer temporality.

We have found clinical measures of periodontal infection to be associated with elevated insulin resistance in a nationally representative, population-based sample of diabetes-free adult men and women. The findings remained after comprehensive multivariable adjustment and strongly suggest a synergistic interaction between oral infection and inflammatory response. Future research that can incorporate direct assessments of exposure to periodontal bacterial species and more comprehensive assessments of inflammation during longitudinal follow-up is necessary for more direct causal inference.

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R.T.D. obtained and analyzed the data and wrote the manuscript. A.S. analyzed the data and wrote the manuscript. P.N.P., M.R., W.T.F., and M.D. wrote, reviewed, and edited the manuscript. D.R.J. analyzed the data and wrote, reviewed, and edited the manuscript. R.T.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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