Periodontal Status and Hemoglobin A1C Change: Longitudinal Results from the Study of Health in Pomerania (SHIP)

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**Objective:** Infection might be a type 2 diabetes mellitus risk factor. Periodontal disease is a chronic infection. We hypothesized that periodontal disease was related to hemoglobin A1C (HbA1C) progression in diabetes-free participants.

**Research Design and Methods:** The Study of Health in Pomerania is a population-based cohort in Germany including 2,973 diabetes-free participants (53% women; aged 20-81 years). Participants were categorized into four groups according to increasing baseline periodontal disease levels (percent of sites per mouth with attachment loss ≥ 5 mm, determined *a priori*); sample sizes for each respective category were 1,122, 488, 463 and 479 (241 were edentulous). Mean absolute changes (year five minus baseline) in HbA1C (ΔHbA1C) were regressed across periodontal categories while adjusting for confounders (e.g., age, gender, smoking, obesity, physical activity, family history).

**Results:** Across baseline periodontal disease categories, ΔHbA1C(±SE) values were 0.023±0.002%, 0.023±0.002%, 0.065±0.03% and 0.106±0.03 (% for trend=0.02), yielding an approximate 5-fold increase in the absolute difference of ΔHbA1C when comparing dentate participants in the highest vs. lowest periodontal disease category; these results were markedly stronger among participants with hs-CRP ≥ 1.0 mg/L (interaction p-value=0.01). When comparing individuals who had neither baseline periodontal disease nor deterioration in periodontal status at five years to individuals with both poor baseline periodontal health and longitudinal periodontal deterioration, mean ΔHbA1C values were 0.005% vs. 0.143% (p=0.003).

**Conclusions:** Periodontal disease was associated with five-year HbA1C progression which was similar to that observed for a two standard deviation increase in either waist-to-hip ratio or age in this population.
Chronic infections are a potentially novel risk factor for diabetogenesis(1). Specifically, there is a known association between periodontal infections and type 2 diabetes, although the temporality and mechanisms of this association remain uncertain(2).

To examine the temporality of this association, data from the First National Health and Nutrition Examination Survey (NHANES I) were recently analyzed to explore whether baseline clinical periodontal status predicted incident diabetes among 9,296 initially diabetes free participants(1). It was reported that baseline periodontal status was a strong predictor of incident diabetes during 20 years of longitudinal follow-up. However, the absence of laboratory hemoglobin A1c (HbA1C) or fasting plasma glucose assessments in NHANES I data, precluded examining the influence of periodontal status on glycemia. Consequently, the potential for diagnostic bias remained; i.e., undiagnosed diabetes might have preceded (and caused) baseline periodontal disease, but was subsequently diagnosed and erroneously defined as incident.

To enable a more precise delineation of the natural history of associations between periodontal infections and diabetogenesis, we presently examine whether baseline clinical periodontal status is associated with five-year HbA1C progression among diabetes-free individuals. We test this hypothesis among participants in the Study of Health in Pomerania (SHIP).

RESEARCH DESIGN AND METHODS
SHIP is a population-based prospective cohort in East Germany involving the cities of Greifswald, Stralsund, Anklam and 29 surrounding villages; the 1995 population in this catchment area was 212,157. From each of these cities, German subjects with main residency in the area were randomly drawn, proportional to each community population and stratified by age and gender. A representative sample of 7,008 adults aged 20-79 years was invited to participate. This two-stage cluster sampling method was adopted from the MONICA Project, Augsburg Germany and yielded twelve five-year age strata (20-81 years) for both sexes. After removing 746 individuals (126 died, 615 moved away, 5 had severe medical problems) 6,262 inhabitants were invited. The final sample included 4,310 individuals, yielding a 68.8% participation rate(3). There were 130 passive nonrespondents due to migration and 231 deceased subjects between the two examinations. Of the remaining 3,949 eligible persons, 649 were active nonrespondents and 3,300 subjects were reexamined, resulting in an 83.6% follow-up rate(4). Participants were excluded from the current analysis if they had: i) prevalent baseline diabetes (n=219) – defined as either self-report physician diagnosed or HbA1C ≥ 6.5%; ii) missing HbA1C (n=74); iii) missing periodontal data (n=136)(5); or iv) missing confounder data (n=77). The current analysis included 2793 participants.

The study was approved by the University of Greifswald’s Institutional Review Board. All participants provided written informed consent.

Oral Examination. Calibrated licensed dentists performed the oral examinations, including a full-mouth tooth count. In SHIP-0 the periodontal probe PCP 11 (Hu-Friedy, Chicago, USA) and in SHIP-1 the periodontal probe PCP 2 (Hu-Friedy, Chicago, USA) were used to assess periodontal probing depth (PPD) and clinical attachment loss (AL) for examined teeth. Measurements were taken at four sites per tooth (mesiobuccal, midbuccal, distobuccal, midlingual), using the half-mouth method on the right or left side in alternate subjects. On the same teeth, coronal caries
was scored visually and with the periodontal probe. Caries and missing teeth were registered by surface and DF-T index was calculated according to WHO criteria. Yearly, calibration exercises(6) yielded an intraclass correlation of 0.82 to 0.91 per examiner, and an interrater correlation of 0.84 relative to AL.

**Hemoglobin A1C Measurement.** Nonfasting blood samples were analyzed at one laboratory which participated in the official Germany INSTAND round-robin tests for quality assurance in analytical labs, at least semi-annually, and internal quality controls were measured daily. At both visits, HbA1C was measured by cation-exchange chromatography (HPLC) with spectrophotometric detection (Diamat Analyzer, BioRad, Munich, Germany) and a CV of 1.5%.

**Risk Factor Assessment.** Participants were queried by computer-aided face-to-face interviews on sociodemographic characteristics, medical histories and medication use (i.e., anti-diabetic (Anatomical Therapeutic Chemical (ATC) code A10), and corticoids drugs (ATC codes A01AC, A07EA, D07, D10AA, G01B, H02, M01BA, R01AD)). A self-administered questionnaire assessed region (rural vs. urban) and education level (<10, 10, or >10 years of schooling). Leisure time physical activity was reported as >2 hours/week, 1-2 hours/week, <1 hour/week or no activity and was then converted into METS(7). Smoking behavior was assessed with a validated questionnaire and categorized as never/occasional, former or current smoker(7). Family history of diabetes was determined by asking if parents or siblings suffer from diabetes.

Height and weight were determined using calibrated scales. Waist circumference was measured at the narrowest place between the last rib and the highest part of the abdomen. Hip circumference according to the greatest circumference between the highest point of the iliac crest and the crotch. Blood pressure was measured thrice using a calibrated semi-automatic sphygmomanometer (HEM-705CP, Omron Corporation, Tokyo, Japan); the average of the last two measurements was used for analysis.

High sensitivity C-reactive protein (hs-CRP) was determined in serum by particle-enhanced immunonephelometry (hsCRP kit, Dade Behring Inc.) with a test sensitivity of 0.2 mg/L. Triglycerides were determined enzymatically using reagents from Roche Diagnostics (Hitachi 717, Roche Diagnostics, Mannheim, Germany). Plasma fibrinogen concentrations were assayed according to Clauss using an Electra 1600 analyzer (Instrumentation Laboratory, Barcelona, Spain). White blood cell (WBC) count was measured by the impedance measurement method using the coulter principle (Coulter® MaxM™) (Coulter Electronics, Miami, USA).

**Statistical Analysis.** Analyses were performed using SAS for Windows version 9.2. PROC SURVEYREG was used to generate variance estimates appropriate for the clustered design. Periodontal categorizations were created to provide a meaningful contrast in exposure while maintaining reasonable sample size balance across categories. The primary exposure variable was the percentage of periodontal sites with AL ≥ 5 mm at baseline (%AL≥5) which was determined a priori(5).

Dentate participants were categorized into four groups based on %AL≥5 as follows: i) 1,122 participants without any 5 mm AL who were considered periodontally “healthy” (ALI); ii) 488 participants with %AL≥5 ranging from 1-8% (ALII); iii) 463 participants with %AL≥5 ranging from 9-33% (ALIII); iv) 479 participants with %AL≥5 ranging from 34-100% (ALIV); 241
edentulous participants formed a fifth category (7; 8).

Three alternate periodontal exposure definitions were also considered. First, baseline mean PPD was categorized into four groups as follows: i) $1.04 \leq \text{mean PPD} \leq 2.00$ mm (PPDI); ii) $2.01 \leq \text{mean PPD} \leq 2.34$ mm (PPDII); iii) $2.35 \leq \text{mean PPD} \leq 2.75$ mm (PPDIII); iv) $2.76 \leq \text{mean PPD} \leq 7.25$ mm (PPDIV).

Second, dentate participants were categorized into tooth count tertiles (26-28, 21-25, 1-20); edentulous participants formed a fourth category.

Finally, dentate participants with longitudinal periodontal data were categorized into four groups according to five-year change (follow-up – baseline) in the percentage of sites with AL $\geq 5$ mm ($\Delta\%\text{AL} \geq 5$) as follows: i) $\Delta\text{ALI}$: 565 participants with improving periodontal health ($\Delta\%\text{AL} \geq 5 < 0$); ii) $\Delta\text{ALII}$: 887 participants without any change in periodontal status ($\Delta\%\text{AL} = 0$); iii) $\Delta\text{ALIII}$: 423 participants with $\Delta\%\text{AL} \geq 5$ ranging from 1-8%; and iv) $\Delta\text{ALIV}$: 437 participants with $\Delta\%\text{AL} \geq 5$ ranging from 9-100%.

To address the specificity of any observed associations to periodontal infection, we also assessed the association between percentage of decayed/filled teeth (%DFT) and HbA1c change. Multivariable linear regression models examined the association between periodontal status (baseline and/or change) and absolute five-year HbA1c change ($\Delta\text{HbA1C}$; calculated as year 5 %HbA1C – baseline %HbA1C). Subgroup analyses were performed removing extreme HbA1C changes to reduce the potential for biased statistical inferences due to possible $\Delta\text{HbA1C}$ normality violations. To reduce the potential for age-related confounding, we also performed stratified analyses in three age strata defined by 20-year age ranges (20-39, 40-59, $\geq 60$ years). Interaction models assessed the statistical evidence of effect modification between periodontal status and systemic inflammatory variables.

**RESULTS**

**General Characteristics.** Participants were Caucasian, of mean age (±SD) 48±15 years and 53% female. Baseline periodontal disease (%AL $\geq 5$) was highly correlated with age ($r=0.50$, $p<0.0001$) and was associated with several socio-demographic, behavior/lifestyle and medical variables (Table 1). Among dentate participants, the mean tooth number (excluding 3rd molars) was 21±6 and after age adjustment. On average 17% of sites/mouth had AL $\geq 5$ mm and this was higher among men (18%) than women (13%) ($p<0.0001$).

Among participants with longitudinal periodontal measures (n=2,312), mean absolute five-year change in %AL $\geq 5$ was $2.3\%\pm 14\%$ (p<0.0001) with a range of -75 to 70%. Five-year change in mean PPD was $-0.08\pm 0.50$ mm (p<0.0001). Baseline %AL $\geq 5$ level was weakly and inversely correlated with change in the same variable ($r=-0.05$, p=0.008), while baseline mean PPD was positively correlated with five-year change in %AL $\geq 5$ ($r=0.08$, p=0.0001). Males, current smokers and younger participants were more likely to experience a decline in periodontal health during follow-up.

Mean±SD $\Delta\text{HbA1C}$ was 0.05±0.59% (range -4.2% to 6.5%); 98% of HbA1C changes were $\geq 1.0\%$ and $\leq 1.0\%$. After multivariable adjustment, the following nonperiodontal variables were associated with $\Delta\text{HbA1C}$ (p<0.05): WHR, fibrinogen, hs-CRP, and former smoking (Table 2).

**Baseline Periodontal or Tooth Loss Status and HbA1c Change.** Participants in the fourth vs. first %AL $\geq 5$ category experienced an ~0.08% greater five-year increase in HbA1C ($p=0.02$, Table 3, model 4). $\Delta\text{HbA1C}$ was accelerated by ~0.10% among edentulous, relative to periodontally healthy, participants ($p=0.05$). When comparing $\Delta$-
HbA1C between participants in the fourth vs. first AL category among 20-39 year olds, the absolute difference was 0.08% (p=0.04). Findings were consistent among 40-59 year olds (0.10%, p=0.005) and participants aged 60+ years (0.07%, p=0.27). There was evidence for an interaction between %AL≥5 and hs-CRP (p for interaction=0.01), in which the increase in Δ-HbA1C with higher %AL≥5 was stronger among participants with hs-CRP≥1.0 mg/L than in those with hs-CRP<1.0 mg/L (Figure). Trends were consistent when considering fibrinogen as the effect modifier (p for interaction=0.24) but less clear for WBC (p for interaction 0.66) as shown in the Figure.

Respective Δ-HbA1C changes in the 1st-4th quartiles of mean PPD were -0.001%, 0.050%, 0.033%, and 0.107% (p for trend <0.01 after multivariable adjustment as in Table 3, model 4).

Mean HbA1C changes across four categories of baseline tooth count were 0.09% (26-28 teeth), 0.04% (21-25 teeth), 0.02% (1-20 teeth) and 0.07% (edentulous); p for trend=0.84.

**Longitudinal Changes in Periodontal Status and HbA1C Change.** Five-year change in %AL≥5 (ΔAL) was associated with Δ-HbA1C (Figure A3 of the online supplement). When comparing individuals who were periodontally healthy at both baseline and follow-up to individuals who had poor baseline periodontal health combined with periodontal deterioration during follow-up (AL-IV and ΔAL-IV), the respective mean HbA1C changes in the two groups were 0.005 vs. 0.143% (p=0.003).

Five-year change in mean PPD was not associated with Δ-HbA1C; Δ-HbA1C values across categories of mean PPD change were 0.03%, 0.06%, 0.04% and 0.01%, respectively (p for trend=0.46).

**Percent of Decayed or Filled Teeth and HbA1C Change.** The %DFT was not correlated with %AL≥5; r=-0.02(p=0.36). After multivariable adjustment, HbA1C progression across quartiles of %DFT was: 0.06%, 0.02%, 0.05%, 0.03% (p for trend=0.70).

**CONCLUSIONS**

This is the first study to report that a chronic infection predicts progression of HbA1C among diabetes-free individuals. We report a positive association between clinical periodontal status and five-year HbA1C change among German participants in the Study of Health in Pomerania. When compared to participants considered periodontally healthy, those participants with elevated levels of baseline periodontal disease experienced an approximate 0.08% greater increase in Δ-HbA1C during five years of follow-up. Deteriorating periodontal health during follow-up was also associated with greater increases in Δ-HbA1C. There was evidence of an additive effect of baseline and follow-up periodontal status such that participants with severe baseline periodontal disease coupled with large declines in longitudinal periodontal health experienced an ~0.13% greater increase in five-year Δ-HbA1C relative to participants who were periodontal healthy at both baseline and follow-up. Additionally, the association between periodontal status and Δ-HbA1C was strongest among participants with elevated levels of hs-CRP.

These findings remained after comprehensive adjustment for confounders, which minimized the potential for spurious associations arising from behavioral/life style variations across periodontal disease levels. The results from multivariable models suggest that age was a strong confounder while other covariates had only minimal impact on the results. Additional analyses within age strata were consistent with results from regression models in the full sample and further minimized the potential for age related confounding.
These data advance previous findings from NHANES I, where elevated levels of baseline periodontal disease were associated with an approximate two-fold increase in incident diabetes risk(1). Specifically, our data demonstrate a temporal trend in which periodontal disease predicts accelerated longitudinal change in HbA1C after control for baseline HbA1C levels and among participants deemed to be diabetes free at baseline using a standardized diabetes definition. This greatly minimizes the possibility that elevated blood glucose levels were present prior to, and therefore contributed to, periodontal disease observed at baseline.

The hypothesis that periodontal infections can influence diabetogenesis is biologically plausible and the concept of inflammation-mediated insulin resistance is intriguing(9). Animal models have demonstrated that virulence factors secreted by periodontal pathogens can stimulate production of inflammatory cytokines such as TNF-α(10). Human studies from this population(11) and others(12) support the notion that periodontal infections can induce a state of low-grade chronic inflammation, and periodontal therapy has been shown to decrease systemic inflammation(13). Accordingly, TNF-α can induce a state of insulin resistance(14), and systemic inflammation has also emerged as a novel predictor of incident diabetes(15; 16). The fact that inflammatory adjustments did not remove the association between periodontal status and Δ-HbA1C suggests that these variables might be sufficient but not necessary mediators in the hypothesized causal path between infection and diabetogenesis(17). Alternatively, the observation of a potential interaction between periodontal status and hs-CRP supports the notion that a synergistic combination of both oral infection and systemic immune response, as opposed to a localized oral infection alone, might be necessary for relevant metabolic abnormalities to develop. These subgroup findings require confirmation in other populations.

The observed ~0.08% difference in five-year HbA1C progression between high and low levels of periodontal disease is potentially clinically relevant. This difference was similar to that observed for a two standard deviation increase in either waist-to-hip ratio or age in this population. Moreover, the difference in Δ-HbA1C is on the same order of magnitude as previously reported by intervention studies from the Diabetes Prevention Program Research Group (DPPRG)(18). The DPPRG observed an ~0.15% reduction in Δ-HbA1C over four years among diabetes-free participants receiving either Metformin or lifestyle modification relative to participants receiving placebo; these HbA1C findings translated into either a 31% (Metformin) or 58% (lifestyle modification) reduction in incident diabetes.

We have used clinical attachment loss as an indirect surrogate of cumulative exposure to a specific array of chronic infections. Future studies with periodontal bacterial measures and/or a broader range of chronic infection assessment can clarify the nature of associations between infection and diabetogenesis; these approaches have been illuminating for cardiovascular disease(19; 20). Data on the association between periodontal status and fasting blood glucose levels can further inform our current findings which were limited to HbA1c.

The finding that caries were not associated with Δ-HbA1C enhances the specificity of the oral infection hypothesis. While caries also have a bacterial etiology, they are not typically known to influence systemic inflammation(21).

The observation that edentulous participants demonstrated mean HbA1C increases similar to dentate participants with periodontal disease might appear counterintuitive to the concept of systemic risk induced by bacterial
biofilms on tooth surfaces. However, these findings are consistent with others that have shown edentulous participants to be at elevated risk for atherosclerosis(7; 8), hypertension(22) and diabetes(1). Desvarieux et al. have suggested that once infection-induced systemic damage has occurred, it is not entirely reversible(8). Alternatively, systemic inflammation related to oral infections might not abate after resolution of clinical disease. It is also possible that repeated bacteremic events occurring prior to extraction of periodontally affected teeth, (23) might allow oral pathogens to colonize systemically. Indeed, viable oral pathogens have been identified in atheromatous plaques(24). Therefore, once bacterial species have colonized the host, tooth extraction, by itself, should not impact their future viability and/or pathogenicity. Although these concepts are speculative and cannot be tested in the current study, they are biologically plausible and consistent with the published literature.

We have found elevated levels of periodontal disease, as well as progression of periodontal disease, to be predictors of HbA1C progression in a randomly sampled, population-based study of Germans, over five years of follow-up. These data support the hypothesis that chronic infections might contribute to diabetogenesis. We await longitudinal results from year ten in SHIP, which will allow us to determine if these subclinical HbA1C changes translate into increased risk for incident diabetes. Focused intervention studies will be necessary to make definitive causal inference regarding the potential role of anti-infective therapy in reducing the risk of diabetes. If confirmed, this relationship would be of substantial public health importance given the population prevalence of periodontal infections(25) and the availability of effective periodontal disease therapies.

**ACKNOWLEDGEMENTS**

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**Financial Disclosures:** None reported.
REFERENCES

**Figure Legend**
Mean five-year HbA1c changes across categories of worsening clinical periodontal status (baseline or five-year change) according to levels of systemic inflammation. Study of Health in Pomerania, 1997 – 2006.
All results adjusted for age, gender, region, smoking, BMI, education, systolic blood pressure, triglycerides, physical activity, corticosteroid use, hs-CRP, white blood cell count and fibrinogen. Sample sizes are presented with x-axis category labels as low & high inflammation group, respectively. A) hs-C-reactive protein, p-value for interaction=0.01; p-value for linear trend across periodontal category among dentate participants with high CRP = 0.05; p-value for linear trend across periodontal category among dentate participants with low CRP = 0.73; B) Fibrinogen, p-value for interaction=0.24; p-value for linear trend across periodontal category among dentate participants with high fibrinogen = 0.06; p-value for linear trend across periodontal category among dentate participants with low fibrinogen = 0.63; C) White blood cell count, p-value for interaction=0.66; p-value for linear trend across periodontal category among dentate participants with high WBC = 0.25; p-value for linear trend across periodontal category among dentate participants with low WBC = 0.24.
Table 1. Characteristics Across Categories of Periodontal Disease (% sites with AL ≥ 5 mm), Adjusted for Age and Gender (% or mean±SE): Study of Health in Pomerania, 1997 – 2006.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>AL I (0%±0%)*</th>
<th>AL II (4%±2%)*</th>
<th>AL III (18%±7%)*</th>
<th>AL IV (62%±21%)*</th>
<th>Edentulous</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1122</td>
<td>489</td>
<td>463</td>
<td>479</td>
<td>241</td>
</tr>
<tr>
<td><strong>Socio-demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age†</td>
<td>38±0.3</td>
<td>47±0.5</td>
<td>53±0.5</td>
<td>59±0.5</td>
<td>68±0.7</td>
</tr>
<tr>
<td>Female†</td>
<td>61%</td>
<td>50%</td>
<td>51%</td>
<td>40%</td>
<td>48%</td>
</tr>
<tr>
<td>&lt;9 years education</td>
<td>26%</td>
<td>25%</td>
<td>34%</td>
<td>44%</td>
<td>53%</td>
</tr>
<tr>
<td>9–10 years education‡</td>
<td>49%</td>
<td>53%</td>
<td>51%</td>
<td>45%</td>
<td>41%</td>
</tr>
<tr>
<td>&gt;10 years education†</td>
<td>25%</td>
<td>22%</td>
<td>15%</td>
<td>11%</td>
<td>6%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smokers†</td>
<td>38%</td>
<td>36%</td>
<td>29%</td>
<td>29%</td>
<td>28%</td>
</tr>
<tr>
<td>Current smokers†</td>
<td>13%</td>
<td>24%</td>
<td>31%</td>
<td>42%</td>
<td>42%</td>
</tr>
<tr>
<td>Pack Yrs Smoking†</td>
<td>5±0.4</td>
<td>7±0.6</td>
<td>9±0.6</td>
<td>13±0.6</td>
<td>13.0±0.9</td>
</tr>
<tr>
<td>Physical Activity (mets/day)</td>
<td>1900±28</td>
<td>1950±37</td>
<td>1907±38</td>
<td>1893±40</td>
<td>1797±59</td>
</tr>
<tr>
<td>Region (Urban vs. Rural)‡</td>
<td>63%</td>
<td>63%</td>
<td>62%</td>
<td>54%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>26.7±0.15</td>
<td>26.8±0.19</td>
<td>27.2±0.20</td>
<td>27.3±0.21</td>
<td>27.1±0.31</td>
</tr>
<tr>
<td>Waist-to-Hip Ratio†</td>
<td>0.85±0.002</td>
<td>0.86±0.003</td>
<td>0.87±0.003</td>
<td>0.87±0.003</td>
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</tr>
<tr>
<td>Systolic blood pressure (mm Hg) ††</td>
<td>133±0.6</td>
<td>135±0.8</td>
<td>134±0.8</td>
<td>135±0.9</td>
<td>138±1.3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg) †</td>
<td>83±0.4</td>
<td>85±0.5</td>
<td>85±0.5</td>
<td>84±0.5</td>
<td>82±0.8</td>
</tr>
<tr>
<td>HbA1c (%)‡</td>
<td>5.20±0.02</td>
<td>5.23±0.02</td>
<td>5.28±0.02</td>
<td>5.25±0.03</td>
<td>5.31±0.04</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)*</td>
<td>1.65±0.05</td>
<td>1.83±0.06</td>
<td>1.95±0.06</td>
<td>1.91±0.07</td>
<td>1.76±0.10</td>
</tr>
<tr>
<td>WBC†</td>
<td>6.2±0.07</td>
<td>6.6±0.09</td>
<td>7.0±0.09</td>
<td>6.9±0.09</td>
<td>6.9±0.14</td>
</tr>
<tr>
<td>Fibrinogen† (g/l)</td>
<td>2.84±0.02</td>
<td>2.87±0.03</td>
<td>3.00±0.03</td>
<td>3.07±0.03</td>
<td>3.13±0.05</td>
</tr>
<tr>
<td>hs-CRP† (mg/l)</td>
<td>2.37±0.15</td>
<td>2.13±0.20</td>
<td>2.47±0.21</td>
<td>3.19±0.21</td>
<td>3.00±0.31</td>
</tr>
<tr>
<td>Corticosteroid use</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Family history of diabetes‡</td>
<td>26%</td>
<td>34%</td>
<td>33%</td>
<td>33%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>Dental</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean AL (mm) †</td>
<td>1.4±0.03</td>
<td>2.1±0.04</td>
<td>3.0±0.04</td>
<td>5.0±0.04</td>
<td>NA</td>
</tr>
<tr>
<td>Mean PPD (mm) †</td>
<td>2.1±0.02</td>
<td>2.3±0.02</td>
<td>2.7±0.03</td>
<td>3.3±0.03</td>
<td>NA</td>
</tr>
<tr>
<td>Decayed, Filled Teeth (#)†</td>
<td>6.1±0.08</td>
<td>6.2±0.11</td>
<td>5.6±0.12</td>
<td>4.1±0.12</td>
<td>††</td>
</tr>
<tr>
<td>Decayed, Filled Surfaces (#)†</td>
<td>17.3±0.3</td>
<td>16.6±0.4</td>
<td>14.7±0.4</td>
<td>10.6±0.5</td>
<td>††</td>
</tr>
<tr>
<td>Tooth Count†</td>
<td>22.6±0.2</td>
<td>23.5±0.2</td>
<td>21.5±0.2</td>
<td>16.4±0.2</td>
<td>††</td>
</tr>
</tbody>
</table>

*Unadjusted category specific mean±SE of % AL≥5 mm
†p<0.01;
‡p<0.05;
††Edentulous excluded from specified age and gender adjusted regressions as the value of these dependent variables are perfectly correlated with edentulism.
Table 2. Five-year HbA1c Change Estimates Derived from Multivariable Regression Modeling: Study of Health in Pomerania, 1997 – 2006

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Deviation</th>
<th>HbA1c Change Estimate*</th>
<th>p-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 15 (years)</td>
<td>0.034%</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Waist-to-Hip Ratio</td>
<td>0.09</td>
<td>0.049%</td>
<td>0.003</td>
</tr>
<tr>
<td>Systolic blood pressure 20 (mmHg)</td>
<td>0.01%</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Triglycerides 1.34 (mmol/L)</td>
<td>0.016%</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Physical activity 870 (METS)</td>
<td>-0.011%</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>White Blood Cell Count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1 Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 2</td>
<td>0.047%</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Quartile 3</td>
<td>0.013</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Quartile 4</td>
<td>0.011</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1 Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 2</td>
<td>0.055%</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Quartile 3</td>
<td>0.052%</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Quartile 4</td>
<td>0.119%</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Hs-CRP &lt; 1.0 mg/L</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0 ≤ hs-CRP &lt; 3.0 mg/L</td>
<td>0.060%</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Hs-CRP ≥ 3.0 mg/L</td>
<td>0.033%</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Periodontal Status††</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1% – 8%</td>
<td>-0.004%</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>9% – 33%</td>
<td>0.020%</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>34% – 100%</td>
<td>0.093%</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Edentulous</td>
<td>0.071%</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-0.002%</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>0.075%</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never, occasional</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>-0.069%</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>-0.053%</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Educational Level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 years</td>
<td>0.055%</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>&lt; 10 years</td>
<td>0.036%</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>Family History of Diabetes (Ref=No hx)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.041%</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Estimates correspond to a 1 standard deviation increase in continuous variables or a change relative to the reference category. Results are simultaneously adjusted for all variables included in the table. Participants missing data for either family history of diabetes, fibrinogen, WBC, CRP or CRP >10.0 mg/L excluded (n=569).
†Significance levels account for the stratified, clustered sampling design in SHIP.
††The percent of sites per mouth with attachment loss ≥ 5 mm
Table 3. Mean±SE HbA1c Change Across Increasing Categories of Baseline Periodontal Disease (% of sites with attachment loss ≥ 5 mm): Study of Health in Pomerania, 1997 – 2006

<table>
<thead>
<tr>
<th>Model</th>
<th>AL I (0%±0%)*</th>
<th>AL II (4%±2%)*</th>
<th>AL III (18%±7%)*</th>
<th>AL IV (62%±21%)*</th>
<th>Edentulous</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1122</td>
<td>N=488</td>
<td>N=463</td>
<td>N=479</td>
<td>N=241</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-0.035±0.017</td>
<td>0.017±0.026</td>
<td>0.097±0.025</td>
<td>0.162±0.029</td>
<td>0.225±0.047</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>0.017±0.018</td>
<td>0.022±0.026</td>
<td>0.071±0.026</td>
<td>0.109±0.030</td>
<td>0.130±0.051</td>
<td>0.009</td>
</tr>
<tr>
<td>3</td>
<td>0.020±0.018</td>
<td>0.023±0.026</td>
<td>0.064±0.026</td>
<td>0.105±0.030</td>
<td>0.136±0.050</td>
<td>0.013</td>
</tr>
<tr>
<td>4</td>
<td>0.023±0.018</td>
<td>0.023±0.027</td>
<td>0.065±0.026</td>
<td>0.106±0.030</td>
<td>0.124±0.052</td>
<td>0.025</td>
</tr>
<tr>
<td>5</td>
<td>0.020±0.017</td>
<td>0.020±0.024</td>
<td>0.080±0.022</td>
<td>0.090±0.028</td>
<td>0.143±0.048</td>
<td>0.011</td>
</tr>
<tr>
<td>6</td>
<td>0.032±0.039</td>
<td>0.029±0.035</td>
<td>0.043±0.040</td>
<td>0.107±0.042</td>
<td>0.110±0.073</td>
<td>0.02</td>
</tr>
<tr>
<td>7</td>
<td>0.024±0.026</td>
<td>0.021±0.031</td>
<td>0.045±0.029</td>
<td>0.117±0.040</td>
<td>0.100±0.052</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>8</td>
<td>0.012±0.018</td>
<td>0.019±0.023</td>
<td>0.071±0.026</td>
<td>0.098±0.026</td>
<td>0.101±0.043</td>
<td>0.013</td>
</tr>
<tr>
<td>9</td>
<td>0.012±0.017</td>
<td>0.014±0.022</td>
<td>0.061±0.024</td>
<td>0.088±0.026</td>
<td>0.071±0.041</td>
<td>0.038</td>
</tr>
<tr>
<td>10</td>
<td>-0.022±0.015</td>
<td>-0.012±0.019</td>
<td>0.039±0.022</td>
<td>0.068±0.022</td>
<td>0.031±0.034</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Model 1: Unadjusted
Model 2: Adjusted for age, gender and region
Model 3: Model 2 + smoking and WHR
Model 4: Model 3 + education, systolic blood pressure, triglycerides and physical activity (n=10 participants excluded due to missing triglyceride data)
Model 5: Model 4 + natural log of baseline HbA1c
Model 6: Model 4 + hs-CRP, WBC, fibrinogen and corticosteroid use (n=146 participants excluded due to missing data on hs-CRP, WBC or Fibrinogen; additional n=78 excluded due to hs-CRP >10 mg/L)
Model 7: Model 6 + family history of diabetes (parent or sibling; n=408 participants excluded due to uncertain family history) (n=54 participants reported corticosteroid use)
Model 8: Model 4 adjustments removing n=8 participants with HbA1c change <-3.0% or > 3.0%
Model 9: Model 4 adjustments removing n= 21 participants with HbA1c change <-2.0% or > 2.0%
Model 10: Model 4 adjustments removing n= 157 participants with HbA1c change <-1.0% or > 1.0%

*Category specific mean±SE of % AL≥5 mm
†P-value for linear trend across dentate participants. All Standard errors and significance levels account for the stratified, clustered sampling design in SHIP.