Periodontal disease, but not edentulism, is independently associated with increased plasma fibrinogen levels

Results from a population-based study

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Summary
The systemic response to periodontal disease was analyzed in the cross-sectional Study of Health in Pomerania (SHIP). The completed data of 2,738 subjects aged 20 to 59 years were used for logistic regression analysis with an increased plasma fibrinogen level (≥3.25 g/L according to Clauss) as the dependent variable. Participants were divided into four groups according to the number of periodontal pockets ≥4mm (0, 1-7, 8-14, ≥15 pocketing). An additional group comprised the 52 edentulous subjects. The adjusted odds ratio (OR) of ≥15 periodontal pockets for increased plasma fibrinogen levels was 1.88 (95% CI: 1.25-2.83). Edentulism per se was not associated with increased plasma fibrinogen levels but was contained in a two-way interaction with the number of cigarettes/day in current smokers (p = 0.031). For edentulous nonsmokers the adjusted OR was 1.10 (95% CI: 0.51-2.39). Furthermore, body mass index, the interaction between gender and body mass index, serum LDL cholesterol, medication, the interaction between LDL cholesterol and medication, aspirin, smoking, school education, chronic bronchitis, and the interaction between alcohol consumption and chronic gastritis were associated with plasma fibrinogen levels. Our results show that periodontal disease but not edentulism per se is associated with an increased plasma fibrinogen level.

Keywords
Fibrinogen, periodontal disease, Study of Health in Pomerania, SHIP

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Introduction
Chronic infections have recently been discussed as a risk factor for coronary artery disease. Micro-organisms suspected of causing atherosclerotic end-points include chlamydia pneumoniae or helicobacter pylori (1, 2). Periodontal disease, another chronic infection caused by Gram-negative bacteria raised similar queries and elicited similar controversial results. Several studies have reported associations between periodontal infections and cardiovascular disease outcomes (3-5). However, these findings could not always be confirmed (6, 7). One mechanism which may explain the relationship between periodontal disease and atherosclerosis was provided by a mouse model. A long-term systemic challenge with Porphyromonas gingivalis accel-
erated the progression of atherosclerotic plaques by causing increased systemic levels of pro-inflammatory factors such as interleukin-1β and serum amyloid A (8). Epidemiological evidence exists, and demonstrates that inflammatory markers are independent risk factors for coronary artery disease and acute myocardial infarction (9-14). Particularly for population-based studies, the use of plasma fibrinogen levels are recommended as a marker for inflammation with regard to the risk of cardiovascular disease (15, 16). The characteristic patterns of change in plasma concentrations (17) suggest that fibrinogen could be even more suitable than high-sensitivity C-reactive protein to reflect agent-host relationships.

If the current status of periodontal disease, but not edentulism per se, is related to plasma fibrinogen level, then the hypothesis of a causal relationship between periodontal disease and coronary heart disease would be supported.

The aim of this population-based study was to investigate the relationship between periodontal pockets, edentulism and plasma fibrinogen levels and to detect independent risk factors for elevated plasma fibrinogen levels.

Materials and methods

The Study of Health in Pomerania (SHIP) is a cross-sectional study in West Pomerania, a region in the northeast of Germany (18). From the total population of 212,157 living in the study area, a random sample was drawn. The sample was selected using resident registration data and performed in two steps. Firstly, the three cities of the region (with 17,076 to 65,977 inhabitants) and the twelve towns (with 1,516 to 3,044 inhabitants) were selected, and then of the smaller towns (with less than 1,500 inhabitants), 17 out of 97 were drawn at random. Secondly, from each of the selected communities, subjects were drawn at random, proportional to the population size of each community and stratified by age and gender. Only individuals with German citizenship and main residency in the study area were included. Finally, 7,008 subjects were sampled, with 292 persons of each gender in each of the twelve five-year age strata. In order to minimize drop-outs by migration or death, subjects were selected in two waves. The net sample (without migrated or deceased persons) comprised 6,267 eligible subjects. Selected persons received a maximum of three written invitations. In cases where the person did not respond, letters were followed by a phone call or by a home visit, if contact by phone was not possible. The final SHIP sample comprised 4,310 participants (68.8% of eligible subjects). The data collection and instruments consisted of four parts: medical examination, oral health examination, health-related interview, and health- and risk-factor-related questionnaire. Data were collected between October 1997 and May 2001. All participants gave informed written consent.

The present analysis was limited to persons aged between 20 and 59 years (response 71.6%). One hundred and sixty-six subjects who had missing data for different reasons (96 subjects without low density lipoprotein (LDL) cholesterol values, 48 subjects without plasma fibrinogen values) were excluded. This resulted in a final study population of 2,738 subjects (1,276 men, 1,462 women) who were available for the present analysis.

Plasma fibrinogen concentrations were assayed according to Clauss (19) using an Electra 1600 analyzer (Instrumentation Laboratory, Barcelona, Spain). The laboratory reference range was 1.7-3.2 g/L. The current status of periodontal disease was assessed by probing depth half mouth. The examination was performed by trained dentists, either on the left or right quadrants (20). All fully erupted teeth, except third molars, were assessed resulting in a maximum of 14 teeth per subject. Probing depths [mm] were examined with a periodontal probe (PCP 11, Hu-Friedy) at mesiobuccal, midbuccal, and midlingual aspects on each selected tooth. Participants were divided into four groups according to the number of periodontal pocketing ≥4mm (0, 1-7, 8-14, ≥15 pocketing). The fifth group consisted of edentulous persons with an additional variable of its own to differentiate zero pockets due to edentulism from zero pockets due to absent periodontal disease.

For the analysis, a set of potential confounder variables was selected. From the interview we included: age (continuous), gender (reference: male), current smoking (cigarettes/day; the number of cigarettes consumed daily was set at 0.5 in occasional smokers with <1 cigarettes/day), former smoking (4 categories: never (reference), <1, 1-9, ≥10 cigarettes/day), alcohol consumption on the last weekend (4 categories: 0 g (reference), 1-150 g, 151-300 g, >300 g), physical activity (reported vigorous exercise once a week or more) (yes/no), SHIP field center (2 categories), localization (urban or rural), certain chronic diseases during the past year (yes/no): gastritis, bronchitis, phlebitis, thrombosis, kidney disease, arthrosis, osteoporosis, pancreatitis, osteoporosis, thyroiditis, cancer, liver cirrhosis, and cholelithiasis. Diabetes mellitus was defined by a positive history of diabetes or hemoglobin (Hb)A1c levels >7% (yes/no). The use of any medication was documented in the interview (yes/no). In addition, the Anatomical-Therapeutic-Chemical (ATC) code was used to assess the medication. The following drugs were considered: vitamin-K antagonists (B01AA), heparin (B01AB), platelet aggregation inhibitors, excl. heparin (B01AC), ACE inhibitors (C09A, C09B), angiotensin-II antagonists (C09C, C09D), HMG-CoA reductase inhibitors (C10AA), fribates (C10AB), oral contraceptives, hormone replacement therapy (G03A, G03C, G03D, G03F), systemic glucocorticoids (H02AB), antibiotics (J01), non-steroidal anti-inflammatory drugs (M01A), salicylic acid and its
derivates (N02BA). From the medical examination we selected
body mass index (BMI; kg/m²), weight, systolic and diastolic
blood pressure (mm Hg). Among the laboratory serum param-
ters total cholesterol (mmol/L), high density lipoprotein (HDL)
cholesterol (mmol/L), LDL cholesterol (mmol/L), the LDL/р
HDL ratio, triglycerides (mmol/L) and HbA1c (%) entered the
analyses. Since diabetes is a known risk factor for periodontal
disease (21, 22), diabetes was forced into the model regardless
of the significance.

Data on quantitative characteristics are expressed as median
and inter quartile range or 25th – 50th – 75th percentile (smok-
ing). Data on qualitative characteristics are expressed as percent
values or absolute numbers as indicated. Comparisons among
groups were made using Kruskal-Wallis’s H-test (continuous
data) and chi²-test (nominal data), pairwise comparisons were
performed with Mann-Whitney’s U-test (continuous data) and
chi²-test (nominal data). Persons belonging to the top quartile of
the plasma fibrinogen level were defined as cases. Odds ratios
(OR) with 95% confidence intervals (CI) were calculated for
this end-point. In all, three logistic regression models were run.
Firstly, the selected variables were reduced to a basic set by
different selection procedures, as described elsewhere (23).
Secondly, three-way and two-way interactions between the var-
iables were assessed. Finally, the variables “periodontal pocket-
ing” and “edentulism” were entered into the model and the
interactions including the new variables were assessed once
more. A value of p <0.05 was considered statistically significant
with one exception, interactions were allowed to enter the
model if the likelihood ratio attained a statistical significance of
p <0.10 (24). The significant three-way interactions were calcu-
lated but not listed. Several additional analyses were done for
each gender to include women-specific factors such as meno-
pause, the use of oral contraceptives or hormone replacement
therapy. Analyses were also repeated for current, former and
never smokers, respectively. All statistical analyses were per-
formed with SPSS software, version 11.0.

Results

Persons with plasma fibrinogen levels of 3.25 g/L or higher
belonged to the top quartile of the plasma fibrinogen distribu-
tion. Among the final sample of 2,738 individuals, 685 persons
met this criterion and were defined as cases. Table 1 shows the
baseline characteristics with respect to the status of increased
plasma fibrinogen level. Subjects with increased plasma
fibrinogen levels were older, more often of female gender, and
more often smokers than subjects without elevated plasma
fibrinogen concentrations. Cases were less educated, consumed
less alcohol, had more often from chronic bronchitis, and
used medication in general more often, ACE inhibitors and
HMG-CoA reductase inhibitors. Furthermore, they exhibited a
higher BMI, a higher systolic and diastolic blood pressure, high-
er serum levels of total cholesterol, LDL cholesterol, triglyce-
drides, and HbA1c, as well as a higher LDL/HDL ratio, but lower
serum levels of HDL cholesterol. Females with increased plas-
ma fibrinogen levels used oral contraceptives or hormone
replacement therapy less often (Table 1). Among the dental
variables, persons with increased plasma fibrinogen levels had
periodontal pockets more often and were more often edentulous
than those without (Table 1).

The following variables were excluded from the logistic
models due to multicollinearity or inefficiency: systolic and dia-
stolic blood pressure (with BMI), HbA1c (with BMI and LDL
cholesterol), total cholesterol and triglycerides (with LDL cho-
lesterol), HDL cholesterol (with LDL cholesterol and BMI). Age,
gender, smoking status, school education, chronic bronchitis
and gastritis, alcohol consumption, diabetes, antidiabetic and
general medication, ATC code N02BA, BMI and LDL choleste-
rol were included in the 1st logistic regression model. The
remaining variables did not attain statistical significance.
Detailed analyses of the final model showed no relevant
problems of multicollinearity.

The results of the logistic regression model with two-way
interactions are given in Table 2. As hypothesized, periodontal
disease was independently associated with increased plasma
fibrinogen levels, which were higher in individuals with ≥15
periodontal pocketing compared to individuals without pockets.
The number of periodontal pockets was not contained in any of
the interactions tested.

Edentulism per se did not independently predict increased
plasma fibrinogen levels. However, edentulism interacted with
smoking. The effect of smoking on plasma fibrinogen concen-
trations was stronger in edentulous than in dentate subjects; the
OR for the smoking status was higher and increased more rap-
idly in edentulous persons (OR for 0; 5; 10; 15 cigarettes/day
1.10; 2.08; 3.93; 7.41) than in dentate subjects (OR for 0; 5; 10;
15 cigarettes/day 1.00; 1.23; 1.51; 1.85). Furthermore, there
was a three-way interaction between edentulism, smoking and
the use of any medication (p = 0.001). The rapidly increasing
effect on plasma fibrinogen levels due to the number of ciga-
rettes/day was only observed in edentulous subjects without
medication (Fig. 1).

Interactions of periodontal pocketing with other variables
were not found. An interaction between smoking and periodon-
tal pocketing was not detected despite the use of different cate-
gorical variables or continuous variables for current smoking
habits. Also, former smoking did not interact with periodontal
disease in an additional analysis. Analyses among healthy, never
smokers were recommended to improve the confounding (25).
For persons who never smoked and were without medication
(n = 321), the OR was 7.85 (p = 0.004) for ≥15 periodontal
pocketing.

Further results of the logistic regression merit consideration.
Current chronic bronchitis was independently related with

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Table 1: Baseline characteristics of study participants with respect to increased plasma fibrinogen levels. BMI denotes body mass index, LDL denotes low density lipoprotein, HDL denotes high density lipoprotein, HbA1c denotes hemoglobin A1c. Values are number (percentage), median ± interquartile range, or 25th - 50th - 75th percentiles. * details are given for females (n = 1462).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Plasma fibrinogen level &lt; 3.25 g/L</th>
<th>Plasma fibrinogen level ≥ 3.25 g/L</th>
<th>P (unadjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>2053</td>
<td>685</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>39.9 ± 18.7</td>
<td>45.5 ± 18.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender, female</td>
<td>1047 (51.0)</td>
<td>415 (60.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (current), Cig./day</td>
<td>0-9</td>
<td>0-0-15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>School education</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>385 (18.8)</td>
<td>223 (32.6)</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>1213 (59.1)</td>
<td>386 (56.4)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>455 (22.2)</td>
<td>76 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption during the past weekend</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0g</td>
<td>615 (30.0)</td>
<td>328 (47.9)</td>
<td></td>
</tr>
<tr>
<td>1-150g</td>
<td>1255 (61.1)</td>
<td>318 (46.4)</td>
<td></td>
</tr>
<tr>
<td>151-300g</td>
<td>171 (8.3)</td>
<td>35 (5.1)</td>
<td></td>
</tr>
<tr>
<td>&gt; 300g</td>
<td>12 (0.6)</td>
<td>4 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Chronic gastritis</td>
<td>118 (5.7)</td>
<td>42 (6.1)</td>
<td>0.707</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>64 (3.1)</td>
<td>42 (6.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>74 (3.6)</td>
<td>36 (5.3)</td>
<td>0.071</td>
</tr>
<tr>
<td>General Medication</td>
<td>1145 (55.8)</td>
<td>448 (65.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vitamin K antagonists</td>
<td>6 (0.3)</td>
<td>5 (0.7)</td>
<td>0.156</td>
</tr>
<tr>
<td>Heparin</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Platelet aggregation inhibitors</td>
<td>19 (0.9)</td>
<td>10 (1.5)</td>
<td>0.279</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>86 (4.2)</td>
<td>57 (8.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angiotensin-II antagonists</td>
<td>26 (1.3)</td>
<td>9 (1.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>42 (2.0)</td>
<td>25 (3.6)</td>
<td>0.022</td>
</tr>
<tr>
<td>Fibrates</td>
<td>12 (0.6)</td>
<td>2 (0.3)</td>
<td>0.539</td>
</tr>
<tr>
<td>Oral contraceptives or hormone replacement therapy*</td>
<td>402 (38.4)</td>
<td>126 (30.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>14 (0.7)</td>
<td>9 (1.3)</td>
<td>0.144</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>24 (1.2)</td>
<td>14 (2.0)</td>
<td>0.093</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>86 (4.2)</td>
<td>33 (4.8)</td>
<td>0.516</td>
</tr>
<tr>
<td>Salicylic acid and derivatives</td>
<td>107 (5.2)</td>
<td>30 (4.4)</td>
<td>0.419</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.4 ± 5.7</td>
<td>28.2 ± 7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.40 ± 1.48</td>
<td>5.86 ± 1.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL Cholesterol, mmol/L</td>
<td>3.23 ± 1.41</td>
<td>3.72 ± 1.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL Cholesterol, mmol/L</td>
<td>1.42 ± 0.56</td>
<td>1.40 ± 0.62</td>
<td>0.017</td>
</tr>
<tr>
<td>LDL/HDL ratio</td>
<td>2.25 ± 1.43</td>
<td>2.62 ± 1.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.34 ± 1.17</td>
<td>1.47 ± 1.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>128.7 ± 24.7</td>
<td>132.2 ± 25.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>81.7 ± 15.3</td>
<td>83.7 ± 14.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.10 ± 0.70</td>
<td>5.30 ± 0.80</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
increased plasma fibrinogen levels. Data also obtained a tendency towards a U-shaped relationship between alcohol drinking and plasma fibrinogen levels. Alcohol consumption up to 300 g on the previous weekend had protective effects against plasma fibrinogen levels compared to no alcohol drinking during the previous weekend. Furthermore, alcohol drinking interacted

Table 1: Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>Plasma fibrinogen level &lt; 3.25 g/L</th>
<th>Plasma fibrinogen level ≥ 3.25 g/L</th>
<th>P (unadjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pockets</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td>720 (35.1)</td>
<td>181 (26.4)</td>
<td></td>
</tr>
<tr>
<td>1 - 7</td>
<td>1004 (48.9)</td>
<td>337 (49.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>8 - 14</td>
<td>227 (11.1)</td>
<td>100 (14.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 15</td>
<td>102 (5.0)</td>
<td>67 (9.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Edentulism, yes</td>
<td>27 (1.3)</td>
<td>25 (3.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2: Coefficients, p-values, odds ratios and their 95% confidence intervals of the two-way interaction model for increased plasma fibrinogen level (≥ 3.25 g/L), n = 2,738, R² (Nagelkerke) = 0.24. OR denotes odds ratio, CI denotes confidence interval. BMI denotes body mass index, LDL denotes low density lipoprotein.
A high educational level and the use of aspirin were inversely associated with elevated plasma fibrinogen levels.

The analysis revealed two further interactions. Firstly, the use of any medication modified the dependence of plasma fibrinogen concentrations on the serum LDL cholesterol concentrations (Table 2). Secondly, an interaction between BMI and gender was found. For the illustration of this interaction, the observed BMI values were cut using the median (26.1 kg/m²; Fig. 3). The effects of BMI on plasma fibrinogen concentrations were stronger in women than in men.

The logistic regression models were re-analyzed with different variations of the variable age (categorized and continuous, age²) in order to control for this confounding. These analyses yielded similar results with respect to the hypothesized association; periodontal pocketing remained an independent risk factor for elevated plasma fibrinogen concentrations in all of these models.

The analysis was also repeated ignoring problems of multicollinearity or inefficiency by including systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, triglycerides and HbA1c. The OR for ≥15 pockets was slightly altered to 1.881 (p = 0.003 for this category, p = 0.027 over all periodontal categories).

The numerical value of the 75% percentile in our sample which we used as the cut-off point was 3.25 g/L. This value corresponds with the upper limit of the reference range for plasma fibrinogen concentration according to Clauss which is given by the method used in the present analysis (1.7-3.2 g/L). Only six persons (0.22%) had values >3.20 g/L and <3.25 g/L. To check for sensitivity of our results with respect to the choice of cut-off point, we repeated the analysis using the upper value of the laboratory reference range instead of the 75% percentile. The results of the logistic regression analyses were similar with respect to the association between the dental variables and increased plasma fibrinogen levels.

**Discussion**

The present study provides evidence for an independent relationship between the number of periodontal pockets and plasma fibrinogen level. Additionally, a relationship between edentulism and plasma fibrinogen concentration in the interaction with smoking was found. Edentulism per se was not associated with plasma fibrinogen level. These findings further elucidate the biological relationship between periodontal disease and the risk of cardiovascular disease.

The systemic response to periodontal disease has previously been analyzed in two population-based studies (26, 27). Wu et al. (26) found an association between subgingival calculus and elevated plasma fibrinogen levels in the data derived from the cross-sectional NHANES III study. Another report from this study (27) demonstrated moderately elevated plasma concentrations...
tions of C-reactive protein in individuals with periodontal pock- eting as well as in edentulous individuals. Some limitations of both studies (26, 27) merit consideration. The sample analyzed by Wu et al. (26) was restricted to individuals who had at least six teeth and was therefore biased by selection. The analyses of Slade et al. (27) did not differentiate between younger and older people with respect to edentulism. Edentulism could be regarded as usual in the sense that the prevalence of edentulism in older people is high, whereas for younger people edentulism tends to be unusual (prevalence ≤15% in the age group). In SHIP, edentulism is unusual in individuals less than 60 years of age (prevalence ≤15% in all five-year age groups). Because of the age restriction in our analysis, a previous severe oral disease can be assumed in those affected persons. To take into consideration the biologic concept of the agent-host-environment (28), it is important to differentiate between usual and unusual tooth loss. The failure to do so could explain for the association of edentulism per se with increased C-reactive protein levels in NHANES III (27). By restricting the age and modelling the interaction between edentulism and smoking, our results concerning the investigated relationship between increased levels of fibrinogen and edentulism are sound. The restriction of the analysis to younger individuals in our study has one further advantage. The association between periodontal disease and cardiovascular disease was reported to be stronger in younger age groups than in the elderly (29, 30). It can be assumed that persons who had increased plasma fibrinogen levels according to our definition (≥3.25 g/L) would exhibit an increased risk for atherosclerosis (13).

In the present study, the current status of periodontal disease was defined by probing depth. The definition of periodontal disease by measuring the percentage of periodontal pockets, as performed in other studies (27), may be problematic; the number of periodontal pockets may decrease with the number of teeth, especially in older persons, whereas the percentage remains constant. Furthermore, BMI, an important confounder for the relationship between periodontal disease and systemic inflammation, was not considered in one analysis (27).

Despite various efforts being made, an interaction between periodontal disease and smoking status on the end-point could not be identified. This confirms the findings of Slade et al. (27). Smoking is one of the most important causes for increased markers of inflammation (13) and is also a major risk factor for periodontitis (21). An attenuation of the effect of smoking on plasma fibrinogen levels was expected by including periodontal pocketing, but the confounding effect was remarkably low (from OR = 1.25; 1.57 and 1.96 to OR = 1.23; 1.51; 1.85 for 5; 10 and 15 cigarettes per day, respectively). The role of smoking on plasma fibrinogen levels is also reflected by the association between chronic bronchitis and plasma fibrinogen concentration which was present in our analysis. This is in agreement with other studies (31, 32). The possible reduction of cardiovascular risk by treating chronic bronchitis with certain antibiotic regimens is currently under debate (33-35). For patients with coronary artery disease the beneficial effect of macrolide treatment in addition to standard therapy seems to be very small (36). However, these findings need to be confirmed on a population-based level.
In concordance with other reports (13, 37-43) a number of factors were associated with increased plasma fibrinogen levels arguing for the good validity of our study. These factors include abstinence from alcoholic beverages (38, 41, 44), chronic gastritis (33), poor education level (13) and higher LDL cholesterol levels (13). The interaction between BMI and gender may not be a contradiction to the observation that fibrinogen levels are consistently found to be higher in women than in men (42). The interactions between smoking and hypertension or diabetes for males, or smoking and LDL/HDL-ratio for females (42), were masked by the interaction between medication and LDL (analysis divided by gender) or were not significant in the present analysis. The interaction between medication and LDL may be explained as an effect of unknown diseases or low compliance. In agreement with other studies (45) the use of aspirin was inversely related to plasma fibrinogen levels in the present study.

In contrast to former studies (13), age was not independently associated with plasma fibrinogen levels. However, significant effects of age on plasma fibrinogen concentrations were detected if school education, LDL cholesterol, BMI or periodontal pocketing were rejected from the logistic regression model. Indeed, the confounding effect of periodontal disease on the association between age and plasma fibrinogen level is plausible as the number of periodontal pocketing increases with age before 40 years (Fig. 4).

To the best of our knowledge, this is the first study which could demonstrate that edentulism per se is not associated with plasma fibrinogen levels. An association was only observed in smokers.

In conclusion, there is an independent association between periodontal disease and plasma fibrinogen levels. These findings further explain the relationship between periodontal disease and cardiovascular disease.

References