

**Periodontitis Increases the Risk of a First Myocardial Infarction:  
A Report From the PAROKRANK Study**

**Running title:** *Rydén et al.; Periodontitis and myocardial infarction*

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## Abstract

**Background**—The relationship between periodontitis (PD) and cardiovascular disease (CVD) is debated. PD is common in patients with CVD. It has been postulated that PD could be causally related to the risk for CVD, a hypothesis tested in PAROKRANK.

**Methods and Results**—805 patients (age <75 years) with a first MI and 805 age (mean 62±8), gender (male 81%) and area matched controls without MI underwent standardized dental examination including panoramic x-ray. The periodontal status was defined as healthy (≥80% remaining bone) or as mild-moderate (79-66%) or severe PD (<66%). Great efforts were made to collect information on possibly related confounders (≈100 variables). Statistical comparisons included Student's pair-wise t-test and Mc Nemar's test in 2x2 contingency tables. Contingency tables exceeding 2x2 with ranked alternatives were tested by Wilcoxon signed rank test. Odds Ratios (95% CI) were calculated by conditional logistic regression.

PD was more common (43%) in patients than in controls (33%;  $p<0.001$ ). There was an increased risk for MI among those with PD (OR = 1.49; 95% CI 1.21-1.83), which remained significant (OR =1.28; 95% CI 1.03-1.60) after adjusting for variables that differed between patients and controls (smoking habits, diabetes, years of education and marital status).

**Conclusions**—In this large case-control study of PD, verified by radiographic bone loss and with a careful consideration of potential confounders, the risk of a first MI was significantly increased in patients with PD even after adjustment for confounding factors. These findings strengthen the possibility of an independent relationship between PD and MI.

**Key words:** periodontitis, panoramic dental radiography (OPG), cardiovascular disease risk factors; myocardial infarction

## Introduction

Cardiovascular disease is a leading mortality cause, which despite a recent decline still contributes to four million deaths/year i.e. almost half of all deaths in Europe whereof about 30% below 65 years<sup>1</sup>. It contributes to 22% of all disability adjusted life years lost in EU and a hospital discharge rate of 2400/100 000 inhabitants<sup>2</sup>. Although traditional risk factors are behind a substantial proportion of cardiovascular disease other factors are important<sup>3</sup>. Chronic inflammation accelerates the progress of atherosclerosis and inflammatory activation increases the risk for plaque rupture leading to acute coronary syndromes<sup>4,5</sup>.

Periodontal diseases are inflammatory conditions ranging from gingivitis to severe periodontitis, the latter with a prevalence of 9% in a western European population<sup>6</sup>. The prevalence is age dependent as exemplified by a survey from the United States where it increased from 11% in the age group 50-65 years to 20% among those >75 years<sup>7</sup>. The disease, which is diagnosed by clinical and radiographic examination<sup>8</sup>, is a chronic tissue-destructive inflammatory state, predominantly induced by Gram-negative bacteria colonizing the gingival crevice<sup>9</sup>.

There is an association between periodontitis and cardiovascular disease<sup>10,11</sup>. The character of this is under debate. An obvious possibility is that the diseases are promoted by shared risk factors, but it has also been postulated, although not confirmed, that periodontitis in itself may cause cardiovascular disease. In support of a causal relationship it has been claimed that periodontal treatment lowers C-reactive protein and low-density lipoproteins and improves endothelial function<sup>12-15</sup>. Such findings, addressing surrogate endpoints and not cardiovascular events, must be interpreted with caution leaving an uncertainty regarding the true nature of the association between periodontal and cardiovascular disease. This knowledge gap was recently

recognized by the American Heart Association (AHA) in the following way ...“*statements that imply a causative association between periodontal disease and specific atherosclerotic vascular disease events or claim that therapeutic interventions may be useful on the basis of that assumption are unwarranted*”<sup>16</sup>.

The hypothesis behind the present investigation, PAROKRANK (Periodontitis and its relation to coronary artery disease), was that there could be an independent relationship between periodontitis and the development of a first myocardial infarction.

## **Material and Methods**

PAROKRANK is a multicentre case-control study, recruiting patients May 2010 - February 2014 at 17 Swedish hospitals. The study centres all had a coronary care unit linked to the Swedish National quality registry SWEDEHEART<sup>17</sup> and a dental care unit at the hospital or in its close proximity. The study was coordinated from the Cardiology Unit, Department of Medicine at Karolinska Institutet, Stockholm.

Patients <75 years hospitalised for a first myocardial infarction according to international criteria<sup>18, 19</sup> were included following informed consent. Exclusion criteria were prior myocardial infarction, prior heart valve replacement and any other condition that, according to the judgement of the investigator, could limit the ability to cope with the protocol.

Controls from the same postcode area as the corresponding patient were randomly selected from the national population registry. They were of the same gender and age ( $\pm$  three months). A list of candidates was generated from which contact was started with the person closest in age. A research nurse at the PAROKRANK coordinating centre approached this person by telephone providing study information and collecting information on the relevant medical

history. To be selected as a control the contacted person had to willing to participate and free from prior myocardial infarction and heart valve replacement. The next person on the list was approached if the first contacted person could not be reached, refused or did not fit the criteria. Contact information to the selected control persons was subsequently sent to the local study centre where written informed consent to participate was obtained. The number of persons approached to recruit one control was about four.

### **Study protocol**

Patients were recruited during their hospital stay and scheduled for outpatient visits six to ten weeks later at the local departments of cardiology and dental medicine. In order to perform the investigations during the same season the matched control persons were contacted usually within ten days after the outpatient visit of their corresponding patients.

Study participants, patients and controls, fasted 12 hours, including no smoking, before the visit at the cardiology department where a physical examination including heart rate, blood pressure following five minutes of rest in sitting position, height, body weight and waist circumference was performed. Venous blood was sampled for the following analyses performed at the local laboratory: complete blood count, P-lipids (total and HDL-cholesterol and triglycerides), P-creatinine, P-fibrinogen, P-glucose and glycated hemoglobin A1c (HbA1c). Study participants without known diabetes underwent an oral glucose tolerance test (75 g glucose in 200 ml water) with venous P-glucose measured in the fasting state and two hours after glucose intake. The point-of-care HemoCue<sup>®</sup> 201 System (HemoCue AB, Ängelholm, Sweden) was used for the P-glucose analysis. High sensitivity C Reactive Protein (hsCRP) was analysed at a central laboratory (redhot diagnostics, Södertälje, Sweden) by means of an ELISA method (MP Biomedicals, New York, USA) intended for quantitative determination CRP, with

the functional sensitivity of 0.1 mg/L. In addition, whole blood (4 ml) and plasma (6 ml) was collected and stored at -70°C in a central bio bank at Karolinska Institutet. A set of questionnaires including information on family and medical history, risk and health preserving factors were completed together with the Montgomery Åsberg Depression Rating Scale<sup>20</sup> (MADRS).

The National quality registry SWEDHEART ([www.swedeheart.se](http://www.swedeheart.se)) was used to amass medical information from the patients at time of their initial hospitalization (RIKS-HIA) and at the secondary prevention follow-up (SEPHIA) 6-10 weeks after the myocardial infarction<sup>17</sup>. The registry was modified to comply with the study needs. Equivalent information was collected for the control population with data entered into a separate database. Smoking habits were defined as current, previous (stopped >1 month ago) or never, and are for patients, as ongoing pharmacological treatment, presented both at the time for hospital admission and follow up.

### **Definitions**

Myocardial infarction was diagnosed by the physician in charge according international criteria on an acute ST or non-ST elevation myocardial infarction as issued during the study period<sup>18, 19</sup>.

The presence of a family history of cardiovascular disease (close relative suffering cardiovascular disease below the age of 60 years) and the presence of peripheral artery, rheumatic, pulmonary and kidney disease as well as cancer and depression was based on self-reported information in standardised questionnaires. The diagnoses hypertension, diabetes and stroke were based on a medical history obtained by the study personnel.

### **Dental examinations**

The dental examination followed a standardized protocol. The maximum number of teeth was 28 since the third molars were excluded. Dentures, complete, partial and a complete implant bridge,

in either jaw were classified as removable dentures. Analogue or digital panoramic radiographs were taken from both dentate and edentulous subjects at the local centres for central analysis at the Department of Dental Medicine, Karolinska Institutet Huddinge by means of a computer program, ImageJ (Image Tool 3.0 software program, Department of Dental Diagnostics Science, University of Texas Health Science Center, Texas, USA). Measurements were carried out with a high-resolution computer monitor in a darkened room. Each tooth was measured at the site with the most pronounced bone loss according. Measurements were, as delineated in **Figure 1**, made from the marginal bone crest to the tooth apex (total bone height) and from the cemento-enamel junction to the tooth apex (total root length) mesially and distally<sup>21</sup>. The arithmetic mean, calculated from the total root length and bone height, was used as a measure of the proportion of remaining bone height supporting each tooth. Measurements were made of all teeth with visible cemento-enamel junctions and visible apices. Dental implants were not examined. Participants were subsequently, based on the mean value of all teeth, allocated to the following groups; healthy ( $\geq 80\%$  remaining bone); mild to moderate periodontitis (79-66%); and severe periodontitis ( $< 66\%$ ). The radiographic examinations were carried out by three dentists blinded to whether the panoramic radiograph came from a patient or control and trained in the use of the equipment. For inter-individual calibration purposes, 42 randomly selected panoramic radiographs were examined. These dental x-rays were graded by three dentists i.e. in 126 separate observations. The three graders were in complete agreement in 121 of these observations (96%). The correlation between dentist 1 and 2 was 0.95, between 1 and 3 0.90 and between 2 and 3 0.90 (Kappa value 0.82).

### **Ethical approval**

The PAROKRANK study was approved by the Regional Ethics Committee at Stockholm

(Dnr:2008/152-31/2) prior to the study and all patients provided written informed consent.

PAROKRANK was conducted according to principles outlined in the Helsinki Declaration.

### **Statistical considerations**

Calculations based on an assumed prevalence of severe periodontitis in the Swedish population<sup>22</sup> supported by an analysis of the first 120 patients and 120 controls in PAROKRANK revealed that to detect an increased risk of myocardial infarction (Odds Ratio = 1.4) among subjects with periodontitis with a power of 80% there was a need for 800 patients and a similar number of matched controls.

Statistical comparisons in order to test differences between the two groups were made by use of the Student's t-test for matched pairs and in order to evaluate hypotheses of variables in 2x2 contingency tables for matched pairs the Mc Nemar's test were used. Contingency tables larger than 2x2 with ranked ordered alternatives were tested by the use of the Wilcoxon signed rank test. Odds Ratios, crude and adjusted for confounders, and corresponding 95% confidence intervals were calculated by use of conditional logistic regression. In addition, descriptive statistics were employed to characterize the data. All analyses were carried out by the use of the SAS system (The SAS system for Windows 9.4, SAS Institute Inc., Cary, NC, USA) and the 5% level of significance was considered. In the case of a statistically significant result the probability value (p-value) has been given.

### **Results**

When first asked 922 patients accepted participation but 117 (13%) withdrew their consent before follow up leaving 805 fully investigated patients and 805 controls according to the protocol. Their mean age was  $62\pm 8$  years and 81% were males.

Clinical characteristics are presented in **Table 1**. Several variables e.g. a history of hypertension, diabetes, kidney and rheumatic disease did not differ between the two groups. A family history of cardiovascular disorders was more common in patients than controls. Compared to the control population smoking was more frequent among patients at admission. Pulmonary diseases (chronic obstructive pulmonary disease (COPD), emphysema and asthma) did not differ between the groups. Of the components COPD was more common among patients than controls (4.4 vs. 1.9%;  $p=0.005$ ). The OGTT disclosed that 74 patients (9.3%) and 42 controls (5.2%;  $p<0.003$ ) had previously undetected diabetes. When added to the participants with already known diabetes (see **Table 1**) the total number of patients and controls with diabetes was 153 (19.1%) and 107 (13.3%;  $p<0.002$ ). The use of cardiovascular treatment (ASA, beta-blockade, renin-angiotensin inhibitors and statins) did not differ significantly when compared between the patients at the time for admission and controls. The use of these drugs were, at the time of follow up, significantly more common among patients than controls, which resulted in a lower blood pressure and lipids among patients than controls (**Table 1**). Factors expressing socio-economic status (**Table 2**) showed a higher number with low education (66 vs. 62%) and a higher rate of divorce among patients (15 vs. 10%).

The number of remaining teeth was  $24\pm 6$  in patients and  $25\pm 5$  ( $p<0.001$ ) in controls. Dental x-rays were available in 797 (99%) of the patients and 796 (99%) of the controls. Mild to moderate or severe periodontitis was present in 43% of the patients and 33% of the controls ( $p<0.001$ ). The distribution on the two groups is presented in **Table 3**. The risk for myocardial infarction was significantly increased among subjects with periodontitis with a crude odds ratio of 1.49 (95% CI: 1.21-1.83). When edentulous participants (patients = 12; controls = 4) were excluded from the analysis of periodontal status the corresponding prevalence were 41 vs. 33%

and the OR for myocardial infarction risk was 1.46 (CI 1.19-1.80). Following statistical adjustments for confounders (diabetes, smoking habits, years of education and marital status) and including edentulous participants there was still a positive association between periodontitis and risk of myocardial infarction with an OR of 1.28 (95% CI 1.03-1.60).

## Discussion

In this large study of the relation between periodontal disease and a first myocardial infarction the risk was significantly increased in patients with moderate to severe periodontitis, objectively verified by radiographic bone loss and with a careful consideration of potential confounders. This finding strengthens the possibility of an independent relationship between periodontitis cardiovascular disease manifestations.

Several cross-sectional and case control investigations have reported on a relation between periodontitis and cardiovascular disease. In an extensive meta-analysis by Blaizot et al<sup>10</sup> the pooled odds ratio from 22 case-control and cross-sectional studies was 2.35 [95% CI 1.87-2.96] and somewhat less in seven cohort studies (OR 1.35 [95% CI 1.27-1.42]). There was, however, a considerable heterogeneity in reported odds ratios from insignificant (OR 1.08 [95% CI 0.77-1.51]) to rather strong (OR 5.14 [95% CI 1.37-19.27]) risk associations in other studies<sup>23, 24</sup>. This discrepancy is reasonably explained by two factors. The first relates to methodological issues such as too small study populations, less strict definitions of periodontitis and information based on data retrieved from registries or questionnaires rather than examinations<sup>25</sup>. The second is a sub-optimal gathering of risk factors such as diet, smoking, overweight, diabetes and stress, important for the development of cardiovascular as well as periodontal disease<sup>26</sup>. Incomplete adjustment for confounders may spuriously reinforce

associations suggesting causality<sup>11, 16, 27</sup>. Thus previous data are, as underlined by the AHA<sup>16</sup>, inconclusive as regards whether the relationship between periodontitis and cardiovascular disease is causal or coincidental and therefore in need of further evaluation.

The ideal study design to provide proof for the assumption that periodontics is causally related to cardiovascular disease is a prospective trial randomly assigning people with periodontitis who are free from cardiovascular disease to dental treatment or to be left untouched and with a composite of cardiovascular death and non-fatal myocardial infarction and stroke as the primary endpoint. Such study does not exist<sup>28</sup> and would be very difficult if at all possible to conduct. The major obstacles are the demands of a very large sample size of screen-detected subjects with periodontitis followed for a long time probably in the magnitude of decades<sup>29</sup>. Moreover it may be considered unethical to deny people with established dental disease treatment. A study design that could provide useful information on associations between various risk markers and myocardial infarction would be a carefully conducted case control study as e.g. demonstrated over the years by the Stockholm Heart Epidemiology Program (SHEEP) a population-based case-referent study of causes of a first myocardial infarction<sup>30-32</sup>. Experiences gained from SHEEP were utilized in the PAROKRANK protocol.

Several design features support the strength of the observed outcome in PAROKRANK, to the best of our knowledge the largest study of its kind. The study population was recruited from a large geographical area with the intention to cover the broadest possible distribution of participants representing a variety of educational and socioeconomic conditions. The cardiovascular disease manifestation was a first myocardial infarction, covering the two expressions of cardiovascular disease possibly influenced by periodontal disease, progressive atherosclerosis and plaque rupture<sup>4, 5</sup>. An upper age limit of 75 years was instituted to avoid a

multiplicity of concomitant disorders in people with more advanced cardiovascular disease. Great emphasis was put on careful characterization of patients and controls ruling out so far less well studied confounders e.g. gluco-metabolic state, socioeconomic factors, stress and mental health and by defining periodontitis with an objective, radiographic method, evaluated at a core center. In order to balance basic disturbing factors, age, gender and geographic location, we matched one control to each patient. In this respect we got two well-balanced groups (**Table 1**). Accounting for previous observations on the importance of diabetes, not only for myocardial infarction but also periodontal disease<sup>33-35</sup>, the presence of diabetes was extensively covered by including participants with previously undetected diabetes. The method used for grading the periodontal disease, digital panoramic radiographs, has a good agreement with other radiographic methods<sup>36, 37</sup> and a good compatibility with other measures of periodontal disease and diagnostic methods<sup>38-40</sup>.

The primary goal of the study was to assess relative risks for first time myocardial infarction based on calculations on odds ratios utilizing patients with myocardial infarction and their controls. When checking for clinically relevant confounders in the univariate and multivariate analyses only factors unaffected by treatment administered to the patients were included. Based on the opinion that the presence of periodontitis in patients and controls are independent of each other we used methods for independent measures when testing our primary hypothesis. Diabetes, smoking habits, years of education and marital status were considered as relevant confounders and therefore included in the adjusted statistical model. Other factors that possibly could be mediators between periodontal and cardiovascular disease, i.e. reflecting reversed causality such as markers of inflammatory activation, were not included and by similar reason MADRS was omitted.

The decision to investigate the patients six to ten weeks after the index infarction had several reasons. First, periodontitis usually starts by the age of 35-40 years and progression to the in PAROKRANK as moderate to severe defined states takes many years<sup>11</sup>. Accordingly a potential difference between patients and controls can be considered independent of this delay. Another and important reason was to avoid the influence of the acute infarction on inflammatory activation and glucose metabolism. Finally, an earlier investigation had to be balanced against the increased risk for bleeding with dental examinations in the immediate post infarction period. Information gained from questionnaires, on the medical history and the use of pharmacological treatment at admission should reflect the period during which the periodontal disease may provoke atherosclerosis and the development of myocardial infarction. As demonstrated in **Table 1** it seems as if such cardiovascular risk factors as hypertension, dyslipidemia, and (known) diabetes had been detected and treated in similar proportions of patients and controls thereby limiting their confounding influence in this, apart from smoking habits, diabetes and family history, fairly homogeneous population.

PAROKRANK showed a positive association between periodontitis and a first myocardial infarction, which remained following adjustment for the differences in clinical characteristics between patients and controls. This strengthens the possibility of an independent relationship between periodontitis and the risk for cardiovascular disease presently expressed as myocardial infarction. There are several possible reasons for a potential causal relationship. Chewing, tooth brushing and dental treatments transfer microorganisms from dental pockets into the blood stream causing bacteraemia and systemic inflammation<sup>11</sup>. This may provoke accelerated atherosclerotic vascular damage, aggregation of platelets and development of thrombotic material, all of which are important for the development of acute myocardial

infarction<sup>41</sup>. DNA from oral microorganisms has indeed been identified in atherosclerotic plaques<sup>42,43</sup>. The outcome of PAROKRANK makes further and more detailed analyses of the character of the association of great interest. Such studies, including a close look at the importance of diabetes and other forms of dysglycaemia and of various inflammatory markers are underway in an attempt to find pathophysiological mechanisms behind the connection between the two diseases.

The ongoing long-term follow-up of PAROKRANK, looking both at risk for recurrent cardiovascular events among cases as well as risks for cardiovascular events among patients and controls with and without periodontitis, will in the light of the present findings be of considerable interest. A positive relationship between the severity of periodontal disease and subsequent cardiovascular events would further strengthen a potential causal character of the relation between periodontitis cardiovascular disease.

### **Strength and limitations**

The careful case control design with patients and controls recruited from a representative sample of Swedish hospitals and with a large number of important variables covered is the major strength of the present study. Another strength is the use of bone loss as an objective indication of the severity of the periodontal disease. Moreover, and to avoid interpretation bias, trained and blinded dentists examined all radiographs centrally according to predefined definitions. Clinical evaluation of periodontitis was also performed, however, not used as a criterion in this study due to difficulties to control the representativity of this type of classification, which is dependent of the investigator to a considerable extent. The major limitation is that PAROKRANK is an observational study, which can support but not prove the concept of a causal relationship. This limitation will, at least partially be overcome by the ongoing follow-up for which Sweden offers

excellent possibilities through the nationwide registries of hospital admissions, myocardial infarctions and coronary interventions. Thus, a follow-up may continue over considerable periods of time, which may be necessary since the contemporary prognosis after a first myocardial infarction is fairly benign<sup>15</sup>.

In conclusion PAROKRANK makes it likely that periodontitis could be looked upon as a risk factor of first time myocardial infarction, which seemingly is independent of a multitude of other risk factors. This observation should increase the interest in preventing and treating periodontal disease with the intention to improve both dental and cardiovascular health in the population.

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**Conflict of Interest Disclosures:** None.

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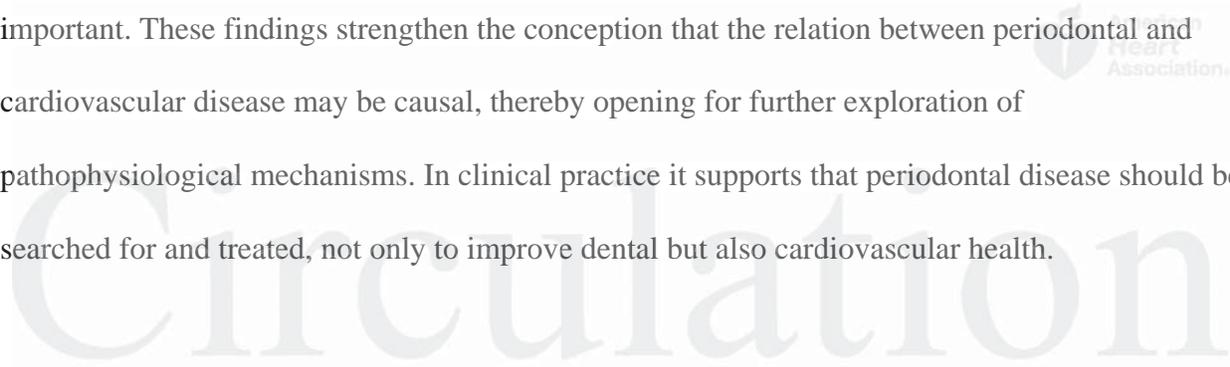
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## Clinical Perspective

PAROKRANK, a Swedish case control study recruiting 805 patients with a first myocardial infarction and the same number of controls matched for age, gender and geographical area, explored whether the relation between periodontitis and cardiovascular disease is related to shared risk factors or if there may be a causal relationship. The presence of periodontitis was significantly higher among patients than controls and the risk to develop myocardial infarction significantly higher in the presence of moderate to severe periodontal disease even after adjustment for potential confounders whereof smoking and dysglycaemia were the most important. These findings strengthen the conception that the relation between periodontal and cardiovascular disease may be causal, thereby opening for further exploration of pathophysiological mechanisms. In clinical practice it supports that periodontal disease should be searched for and treated, not only to improve dental but also cardiovascular health.



**Table 1.** Clinical characteristics. Data are presented as mean  $\pm$  SD or number (%). If not otherwise stated patient data were retrieved at the follow up visit.

Variables	Patients n=805	Controls n=805	p-value
Age (years)	62 $\pm$ 8	62 $\pm$ 8	*
Male gender	654 (81)	654 (81)	*
Known family history of cardiovascular disease	302 (38)	183 (23)	<0.001
Medical history			
Hypertension	285 (36)	268 (34)	0.38
Peripheral artery disease	20 (3)	10 (1)	0.099
Stroke	22 (3)	18 (2)	0.64
Diabetes mellitus	79 (10)	65 (8)	0.25
Rheumatic disease	164 (21)	136 (17)	0.056
Pulmonary disease	106 (14)	85 (11)	0.11
Kidney disease	33 (4)	32 (4)	1.00
Cancer	66 (8)	58 (7)	0.51
Depression	76 (9)	71 (9)	0.73
Smoking habits (patients at admission)			
Current	206 (26)	96 (12)	
Previous	286 (36)	361 (45)	<0.001
Never	297 (38)	348 (43)	
Smoking habits (patients at follow up)			
Current	70 (9)	96 (12)	
Previous	440 (55)	361 (45)	0.22
Never	283 (36)	348 (43)	
Waist circumference (cm)	99 $\pm$ 11	98 $\pm$ 12	0.12
Body Mass Index (kg/m <sup>2</sup> )	27 $\pm$ 4	27 $\pm$ 4	0.24
Blood pressure (mm Hg)			
Systolic	129 $\pm$ 17	137 $\pm$ 17	<0.001
Diastolic	77 $\pm$ 10	84 $\pm$ 10	<0.001
Laboratory			
Cholesterol (mmol/l)	3.9 $\pm$ 0.8	5.5 $\pm$ 1.1	<0.001
Triglycerides (mmol/l)	1.3 $\pm$ 0.9	1.5 $\pm$ 1.3	0.009
HDL-cholesterol (mmol/l)	1.2 $\pm$ 0.3	1.5 $\pm$ 0.4	<0.001
HbA1c (mmol/mol)	41 $\pm$ 8	39 $\pm$ 8	<0.001
Fibrinogen (g/L)	3.4 $\pm$ 0.8	3.2 $\pm$ 0.7	<0.001
High sensitivity CRP (mg/L)	2.3 $\pm$ 2.6	2.2 $\pm$ 2.5	0.48
White blood cell count (x10 <sup>9</sup> /L)	6.6 $\pm$ 4.8	5.7 $\pm$ 3.0	<0.001
Questionnaire (total score)			
MADRS	6.0 $\pm$ 6.2	4.4 $\pm$ 5.1	<0.001
Pharmacological treatment (patients at admission)			
Renin-angiotensin inhibitors	194 (24)	213 (27)	0.29
Aspirin	90 (11)	82 (10)	0.53
Beta-blockers	116 (15)	106 (13)	0.49
Statins	119 (15)	134 (17)	0.37
Antiinflammatory agents (NSAID)	15 (2)	32 (4)	0.019
Corticosteroids	26 (3)	30 (4)	0.89
Pharmacological treatment (patients at follow up)			
Renin-angiotensin inhibitors	687 (86)	213 (27)	<0.001
Aspirin	776 (97)	82 (10)	<0.001
Beta-blockers	735 (92)	106 (13)	<0.001
Statins	775 (97)	134 (17)	<0.001
Antiinflammatory agents (NSAID)	13 (2)	32 (4)	0.007
Corticosteroids	24 (3)	30 (4)	0.39

HDL=high-density lipoproteins, HbA1c=glycated hemoglobin A1c, CRP=C-reactive protein,

MADRS=Montgomery Åsberg Depression Rating Scale

\* = Matching variable, not tested

**Table 2.** Socioeconomic factors. Data are presented as number (%).

Variables	Patients n=805	Controls n=805	p-value
Education			
1-12 years	533 (67)	494 (62)	0.052
University	269 (34)	307 (38)	
Occupation			
Working	420 (52)	395 (49)	0.051
Retired	353 (44)	370 (46)	
Sick leave	10 (1)	4 (1)	
Other	21 (3)	36 (4)	
Annual income (household; SEK/year)			
<180 000	100 (13)	90 (11)	0.048
180 000 – 300 000	226 (28)	192 (24)	
>300 000	468 (59)	516 (65)	
Marital status			
Single	86 (11)	83 (10)	0.046
Married	597 (74)	642 (80)	
Divorced/Widowed	121 (15)	79 (10)	

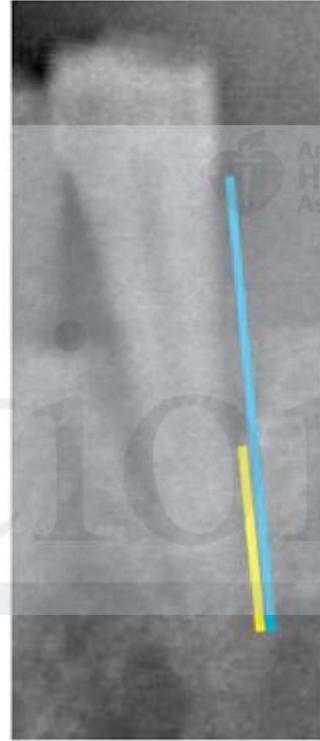
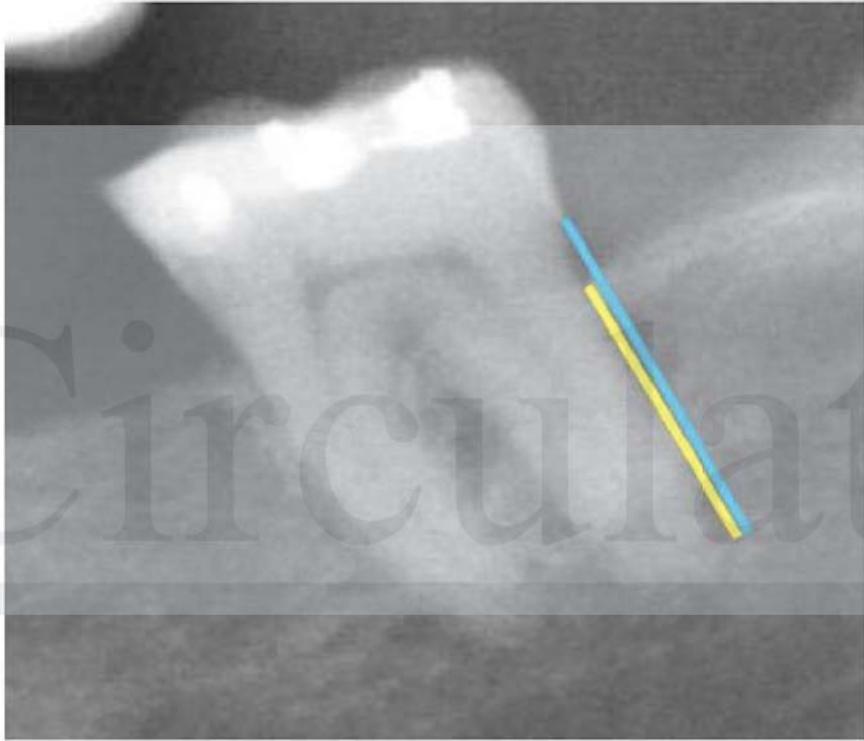
**Table 3.** Periodontal status according to panoramic x-rays\*. Data presented as number (%).

Periodontal status	Patients n=796	Controls n=797	p-value
Healthy	458 (58)	530 (67)	<0.001
Mild-moderate periodontitis	261 (33)	231 (29)	
Severe periodontitis	78 (10)	35 (4)	

\* x-rays not available in 9 patients and 8 controls

### Figure Legend:

**Figure 1.** Radiographic measurements were made from the marginal alveolar bone to the tooth apex (yellow line) and from the cemento-enamel junction to the tooth apex (blue line). The examples show to the left normal bone height and to the right alveolar bone loss.



American Heart Association.

Circulation