

# The clinical course of chronic periodontitis: V. Predictive factors in periodontal disease

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## Abstract

**Background:** The factors associated with initial periodontitis are not well understood and cannot be identified by cross-sectional studies.

**Aim:** To identify the factors associated with the initiation of chronic periodontitis using ante-dependence modelling.

**Material and Methods:** A 26-year longitudinal study of the natural history of periodontitis served as the basis for the study. In 1969, 565 Norwegian men aged 16–34 years were surveyed. Subsequent surveys were performed in 1971, 1973, 1975, 1981, 1988 and finally in 1995, with 223 remaining subjects. Plaque (PII), gingival (GI) and calculus indices (CI) and loss of attachment (LoA) were recorded. Ante-dependence modelling using a Markov chain enabled the results of this sequence of examinations to be analysed longitudinally, taking into account serial dependence, describing temporal changes in patients' levels of disease and allowing for both progression and regression between disease categories.

**Results:** With age, the rate of disease regression decreased. Increasing calculus accumulation and smoking increased the rate of disease progression, while increasing GI increased the rate of regression.

**Conclusions:** Increased mean CI and smoking were significant predictive covariates for progression, while increased mean GI and younger age predicted regression of initial periodontitis.

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## Dedication:

This manuscript is dedicated to the memory of our co-author, Harald Løe, friend, colleague and mentor, who died on 9 August 2008 during the period of the revision of this paper. Without Harald's foresight in carrying out the surveys on the natural history of periodontal disease, this paper would not have eventuated.

Key words: age; ante-dependence model; calculus; disease progression; gingivitis; initial periodontitis; prediction; smoking

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Although it is generally believed that, at some point, periodontitis must be preceded by gingivitis (Løe & Morrison 1986, Page & Kornman 1997), it is also true that not all gingivitis sites progress to periodontitis.

The role of gingivitis in the pathogenesis of chronic periodontitis has been elucidated previously (Schätzle et al. 2003a) in a longitudinal investigation of the initiation and progression of natural periodontal disease in a randomized group of middle-class Norwegian men. This study showed that before 40 years of age, only slight increases in periodontal attachment loss due to pocket formation occurred, but after this, the frequency increased significantly. Loss of attachment (LoA) due to gingival recession was rarely observed. As men approached 60 years of age, gingival sites that consistently bled on probing over the 26 years had approximately 70% more attachment loss than sites

that were consistently non-inflamed [gingival index (GI) = 0].

The fact that sites with non-inflamed gingivae also exhibited some LoA and pocket formation was thought to be due to fluctuations in disease expression during long observational intervals possibly combined with the presence of subclinical inflammation (Schätzle et al. 2003a).

A subsequent analysis of the same cohort of well-maintained and dentally aware Norwegian men (Heitz-Mayfield et al. 2003) revealed that 50% of the 16 year olds exhibited initial LoA on the buccal surfaces of molars and premolars in both the jaws, most of which were "gingival recession". These lesions

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progressed at a relatively slow rate (0.1 mm/year) during their twenties and thirties. At 30 years of age, the mean individual cumulative LoA was <1 mm. As the subjects approached 40 years of age, the mean individual loss was slightly above 1.5 mm (Løe et al. 1978b). Generally, the incidence of incipient periodontal destruction increased with age, with the highest rate occurring between 50 and 60 years. Moreover, while gingival recession was the predominant lesion before age 40, periodontal pocketing was the principal mode of destruction between 50 and 60 years of age (Heitz-Mayfield et al. 2003).

The rate of attachment loss during various stages of adult life was further assessed in a third analysis of the cohort (Schätzle et al. 2003b). This analysis revealed that the annual rates and the annualized risks of periodontal attachment loss vary throughout adult life. The annual mean rate and the mean annualized risk of initial attachment loss were the highest between 16 and 34 years of age. However, most of this was due to recession.

Finally, the fourth study on this cohort of Norwegian men (Schätzle et al. 2004) showed that different severities of gingivitis yielded different risks for tooth loss. Teeth surrounded with healthy gingival tissues were maintained for a tooth age of 51 years, while teeth consistently surrounded with inflamed gingivae yielded a 46 times higher risk of loss. Only two-thirds of such teeth were maintained throughout the 26-year observation period. Based on this observation, gingival inflammation was thought to be a risk factor for tooth loss.

Cross-sectional statistics, however, make it difficult to analyse fluctuations between gingivitis and initial periodontitis. Furthermore, the temporal association between the various factors influencing the initiation of progression and regression between disease states cannot be identified. Owing to the cyclical nature of the disease process, cross-sectional statistics cannot provide a rate at which the patients progress or regress from health (gingivitis) to initial periodontitis and back again.

It is understood that attachment loss or probing depth at a particular time may not be representative of the "activity" of a lesion, in terms of loss and/or gain of clinical attachment that has occurred in the preceding interval. This is especially so in studies of longer duration with lengthy periods between examinations.

Ante-dependence modelling using a Markov chain enables the results of a sequence of periodontal examinations to be analysed longitudinally taking into account serial dependence. This model describes temporal changes in patients' levels of disease in terms of transition probabilities, which allow for both progression and regression of the disease from health/gingivitis to initial periodontitis, and then back again, from initial periodontitis to health/gingivitis. To date, there has only been one 3-year longitudinal study (Faddy et al. 2000) demonstrating how ante-dependence modelling of longitudinal data can reveal effects that may not be immediately apparent from the data, such as smoking and increasing age, inhibiting the "healing process" rather than promoting disease progression.

The purpose of this analysis was to use ante-dependence modelling to identify the factors associated with chronic periodontitis in a 26-year longitudinal study. Chronic periodontitis was defined at a patient level according to the categorization proposed by the 5th European Workshop on Periodontology in 2005 (Tonetti & Claffey 2005).

## Material and Methods

### Sources of data

The information presented in this paper is based on a 26-year longitudinal study of the initiation and progression of periodontal disease in well-educated middle-class men in Norway. As previously alluded to, this cohort received "state-of-the-art" dental care from the age of 3 years and reportedly performed an oral home care programme on a daily basis. The study population has been described earlier (Løe et al. 1978a, b, c, 1986, Ånerud et al. 1991, Heitz-Mayfield et al. 2003, Schätzle et al. 2003a, b, 2004). The initial examination in 1969 included 565 individuals aged between 16 and 34 years. Subsequent surveys took place in 1971, 1973, 1975, 1981, 1988 and 1995. Of the 565 subjects examined in 1969, 223 attended the seventh examination, 26 years later.

Starting shortly after World War I, the City of Oslo launched a comprehensive oral health care programme for the improvement of oral health in its children. From 1936 onwards (Gythfeldt 1937), all children were entitled to comprehensive examinations and treatment on the basis of an annual recall, and by

1946, every school child was offered systematic dental care including preventive, restorative, endodontic, orthodontic and surgical therapy, if needed. Over time, other programmes were added to include both preschool children and university students. Thus, the dental care programme covered the age span from 3 to 23 years.

### Clinical parameters

The examinations were performed in well-equipped clinical facilities at the Faculty of Odontology, University of Oslo, and included assessments of the periodontal tissues. At each appointment, the participants answered questions regarding their personal dental care and smoking habits. Also, at each examination throughout the study, the same oral indices were scored by the same two investigators, both of whom were experienced periodontists, and well standardized and repeatedly calibrated in various disease levels (H. B., Å. Å.).

The following oral indices or measurements were recorded (Løe et al. 1978a):

- GI (Løe & Silness 1963).
- LoA in millimetres (Glavind & Løe 1967).
- Plaque index (PII) (Silness & Løe 1964).
- Retention index (RI) (Løe 1967).

From the survey in 1973 and thereafter, recession of the marginal gingiva was measured on all mesial and buccal surfaces of all teeth as the distance in millimetres from the cement-enamel junction (CEJ) to the gingival margin, whenever located apically to the CEJ. Pocket depth was calculated from the measurements of the attachment level and the gingival recession at each site. In the survey in 1981 and in all subsequent examinations, the distal and lingual surfaces were also included in the examinations. Third molars were not included in the evaluation at any time.

Subjects were also stratified according to their smoking history into self-reported *smokers* and *non-smokers*. The non-smoking cohort was made up of individuals who, at each examination, reported that they had never smoked. The smoking group consisted of all subjects, who, at every survey in which they participated, reported smoking two or more cigarettes per day. However, as the information relating to smokers and non-smokers

collected at the examination in 1995 was lost, it was assumed that participants who were smoking throughout the study (for almost 20 years, respectively) continued to smoke up to 1995.

**Data analyses**

Based on the *consensus* paper at the 5th European Workshop of Periodontology (2005) (Tonetti & Claffey 2005), three stages of periodontal disease corresponding to different levels of LoA were defined as:

- Level 0 – individuals with a healthy periodontium: upto one proximal site with LoA ≥3 mm.
- Level 1 – presence of proximal attachment loss of ≥3 mm in ≥2 non-adjacent teeth.
- Level 2 – presence of proximal attachment loss of ≥5 mm in ≥30% of teeth present.

This categorization was measured for a number of subjects at seven examinations carried out over the 26-year period. As in most longitudinal studies of this size and length, a number of the participants dropped out and hence could not be followed. Other subjects missed one or more examinations, but attended the last survey. The aim of the present analysis was to model the progression and regression (healing) between disease levels or states over the period of the study (1969–1995), in terms of the covariates determined in the previous survey, i.e. age (years), smoking/non-smoking status (binary 0/1), mean PII over all available sites, mean GI over all available sites and mean calculus index (CI) (a component of the RI) over all available sites. Consequently, those with contiguous sequences of examinations starting at baseline comprised the data for this analysis.

**Modelling**

In view of the very small number of subjects whose periodontal disease ever progressed to Level 2, modelling and data analyses were restricted to Levels 0 and 1, i.e. a transition from the category of health to that of initial periodontitis and from initial periodontitis back to health. The Markov model used has been described earlier by Faddy et al. (2000) and may be summarized briefly as follows:

Disease is assumed to progress between stages or Levels 0 and 1 at a rate  $\alpha$  per unit

time, and regress or reverse between Levels 1 and 0 at a rate  $\beta$  per unit time according to a two-state Markov chain in continuous time. This leads to probabilities  $p_{ij}(t)$  of transitions between levels  $i$  and  $j$  in time  $t$  given by the formulae:

$$p_{00}(t) = [\beta + \alpha \exp\{-(\alpha + \beta)t\}] / (\alpha + \beta)$$

$$p_{01}(t) = [\alpha - \alpha \exp\{-(\alpha + \beta)t\}] / (\alpha + \beta)$$

$$p_{10}(t) = [\beta - \beta \exp\{-(\alpha + \beta)t\}] / (\alpha + \beta)$$

$$p_{11}(t) = [\alpha + \beta \exp\{-(\alpha + \beta)t\}] / (\alpha + \beta).$$

The rates  $\alpha$  and  $\beta$  were log-linearly dependent on the covariates according to the formulae:

$$\begin{aligned} \log(\alpha) = & a_0 + a_1 \times \text{age} + a_2 \\ & \times \text{smoking status} + a_3 \\ & \times \text{mean plaque index} + a_4 \\ & \times \text{mean gingival index} + a_5 \\ & \times \text{mean calculus index,} \end{aligned}$$

and

$$\begin{aligned} \log(\beta) = & b_0 + b_1 \times \text{age} + b_2 \\ & \times \text{smoking status} + b_3 \\ & \times \text{mean plaque index} + b_4 \\ & \times \text{mean gingival index} + b_5 \\ & \times \text{mean calculus index.} \end{aligned}$$

To allow for possible changes in these rates of disease progression and regression during the course of the study, some variation in the parameters  $a_0$  and  $b_0$  between examinations was included. All the resulting parameters  $a_0$ 's,  $a_1$ ,  $a_2$ ,  $a_3$ ,  $a_4$  and  $a_5$ ,  $b_0$ 's,  $b_1$ ,  $b_2$ ,  $b_3$ ,  $b_4$  and  $b_5$  were estimated from the observed data by maximum likelihood with backwards elimination used to remove any non-significant covariate effects, using a significance level of 5%. Any interactive effects of smoking status with mean PII, mean GI and mean CI were estimated as additional terms in the above forms of  $\log(\alpha)$  and  $\log(\beta)$ , and included in the model if they were significant at the 5% level.

**Results**

Of the initial 565 individuals, 380 were present at contiguous examinations starting at baseline (i.e. examinations 1, 2, . . . ,  $n$  before dropping out at examination  $n+1$ , for some  $n \geq 2$ ) and were, therefore, included in this analysis. The average times ( $t$ ) between examinations were 25 months (surveys 1–2), 24 months (surveys 2–3), 27 months (surveys 3–4), 76 months (sur-

Table 1. The proportions of transitions between disease levels from survey to survey

Visits 1–4	To: 0	1	2
From			
0	87.0%	5.3%	0%
1	4.7%	3.0%	0%
2	0%	0%	0%
Visits 4–5	To: 0	1	2
From			
0	85.4%	7.8%	0%
1	1.0%	5.8%	0%
2	0%	0%	0%
Visits 5–6	To: 0	1	2
From			
0	63.8%	24.6%	0%
1	1.5%	10.1%	0%
2	0%	0%	0%
Visits 6–7	To: 0	1	2
From			
0	20.4%	50.0%	0%
1	1.8%	24.1%	3.7%
2	0%	0%	0%

Table 2. Baseline demographics

<i>N</i>	380
Age	16–35 years
Proportion of patients with Level-1 disease	6.84%
Smoking	109 (28.7%)
PII mean (range)	1.2 (0.50–1.9)
GI mean (range)	0.89 (0.05–1.8)
CI mean (range)	0.16 (0.00–1.1)

Level 1 = ≥2 mesial sites with LOA ≥3 mm. CI, calculus index; GI, gingival index; PII, plaque index.

veys 4–5), 77 months (surveys 5–6) and 85 months (surveys 6–7), respectively. The proportions of transitions between disease levels between surveys are shown in Table 1.

The baseline demographics of these 380 individuals are shown in Table 2. Over the 26 years of investigation, the subjects' ages ranged from a minimum of 16 years (survey 1) to a maximum of 59 years (survey 7), and the proportions of subjects smoking ( $smk = 1$ ) ranged from 29% at the beginning of the study to 9% at the end. The mean PII ranged from 0.35 to 1.98; the mean GI ranged from 0.018 to 1.84; and the mean CI ranged from 0 to 1.40.

Some changes in the rates of disease progression and regression were apparent during the course of the study (cf Table 1), and estimates of these rates were as follows:

(i) between surveys 1 and 4 :

$$\begin{aligned} \log(\alpha) = & -6.21 + 0.85 \times smk + 1.62 \times CI \\ \log(\beta) = & 21.39 - 0.22 \times \text{age} + 1.57 \times GI \end{aligned}$$

(ii) between surveys 4 and 5 :

$$\log(\alpha) = -7.10 + 0.85 \times \text{smk} + 1.62 \times \text{CI}$$

$$\log(\beta) = -0.42 - 0.22 \times \text{age} + 1.57 \times \text{GI}$$

(iii) between surveys 5 and 6 :

$$\log(\alpha) = -5.96 + 0.85 \times \text{smk} + 1.62 \times \text{CI}$$

$$\log(\beta) = -0.42 - 0.22 \times \text{age} + 1.57 \times \text{GI}$$

(iv) between surveys 6 and 7 :

$$\log(\alpha) = -4.59 + 0.85 \times \text{smk} + 1.62 \times \text{CI}$$

$$\log(\beta) = -0.42 - 0.22 \times \text{age} + 1.57 \times \text{GI}$$

The time periods involved here (surveys 1–4, surveys 4–5, surveys 5–6 and surveys 6–7) were all of some 6–7-year duration. The rates of disease progression show some reduction after survey 4, but after surveys 5 and 6 there are increases, towards higher levels than they were initially, and the rates of disease regression show a reduction after survey 4; these changes are statistically significant with  $p$ -value  $< 0.001$ . Any further changes in the rate of disease regression over the course of the study (after survey 5) were not significant ( $p$ -value  $> 0.2$ ). To some extent, these changes in the rates of progression and regression as the study proceeded reflect the increasing ages of the subjects as there was no additional effect of age on the rates of disease progression ( $p$ -value  $> 0.2$ ), but there was a further negative effect of increasing age, reducing the rates of regression ( $p$ -value  $< 0.001$ ). The other effects, indicated above, of smoking and higher mean CI increasing the rates of disease progression, and of a higher mean GI increasing the rates of regression are all significant ( $p$ -values  $< 0.01$ ), whereas the effects of mean GI on the rate of progression, smoking and mean CI on the rate of regression, and mean PII on both the rates, were not significant ( $p$ -values  $> 0.2$ ). There were no significant additional interactive effects of smoking with mean GI, mean CI and mean PII on the rates of either progression or regression of disease ( $p$ -values  $> 0.2$ ).

In this population, smokers had about twice the rate of disease progression as non-smokers for this particular definition of disease category (Level 1; Tonetti & Claffey 2005). The effect of calculus on the rates of disease progression was such that these were higher by a factor of approximately 5 for CI = 1 compared with CI = 0, and the effect of mean GI on the rates of regression

Table 3. Estimated proportions of the subjects experiencing some disease progression between surveys

Surveys		Non-smokers	Smokers
1–4	CI 0	0.14	0.30
	1	0.54	0.84
4–5	CI 0	0.061	0.14
	1	0.27	0.52
5–6	CI 0	0.18	0.37
	1	0.63	0.90
6–7	CI 0	0.58	0.87
	1	0.987	0.9999

CI, calculus index.

Table 4. Estimated proportions of the subjects experiencing some disease regression between surveys

Surveys		Age	
		30 years	50 years
1–4	GI 0.5	0.58	0.010
	1.5	0.985	0.049
Surveys 4–5	Age	30 years	50 years
	GI 0.5	0.13	0.0017
Surveys 5–6	Age	30 years	50 years
	GI 0.5	0.13	0.0017
Surveys 6–7	Age	30 years	50 years
	GI 0.5	0.15	0.0019
	1.5	0.54	0.0091

GI, gingival index.

was such that these were also higher by a factor of approximately 5 for GI = 1.5 compared with GI = 0.5. Tables 3 and 4 show the estimated proportions of subjects experiencing some disease progression, and some disease regression, respectively, between surveys, for different values of these predictive factors.

In Figs 1 and 2, there are illustrative plots of (a) the estimated rates of disease progression and regression with increasing age, and (b) the corresponding proportions of the subjects experiencing some disease progression, and some disease regression, during the period between surveys 1 and 4, and between surveys 6 and 7.

Figures 1(a) and 2(a) indicate that after certain ages, the declining rates of disease regression have fallen below the rates of disease progression, and disease is more likely to take hold after such critical ages. All of the subjects in survey 1 were younger than these ages, but by survey 6 none of the subjects had rates of disease progression less than

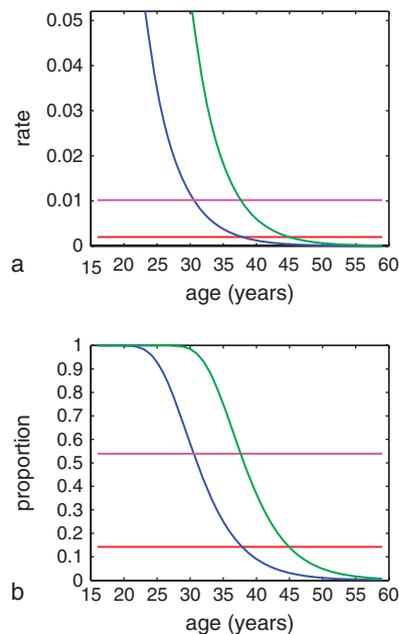


Fig. 1. (a) Estimated rates of disease progression for non-smoking subjects with mean calculus indices 0 (—) and 1 (—), and rates of disease regression for non-smoking subjects with mean gingival indices 0.5 (—) and 1.5 (—), for the period between surveys 1 and 4. (b) Estimated proportions of subjects experiencing some disease progression for non-smokers with mean calculus indices 0 (—) and 1 (—), and proportions of subjects experiencing some disease regression for non-smokers with mean gingival indices 0.5 (—) and 1.5 (—), during the period between surveys 1 and 4.

rates of disease regression. An increase in the mean GI from 0.5 to 1.5 results in an increase of this critical age (i.e. disease tends to take hold later) by some 7–8 years, as does a decrease in the mean CI from 1 to 0. And for smokers, this age is lower (i.e. disease tends to take hold earlier) than that for non-smokers by some 3–4 years.

### Discussion

The Norwegian population analysed in the present study has had the benefit of a comprehensive oral health care programme from an early age (3 years). All the subjects participating in this study had been in the City of Oslo's Dental Program and subsequently reported to have seen their private dentists on a regular annual basis. There must be very few other population groups in the world, which in 1995 and at ages up to almost 60 years had documented an exposure to systematic dental care similar to that of

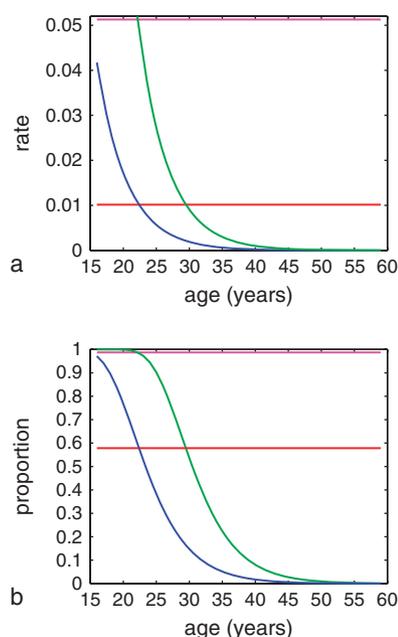


Fig. 2. (a) Estimated rates of disease progression for non-smoking subjects with mean calculus indices 0 (—) and 1 (—), and rates of disease regression for non-smoking subjects with mean gingival indices 0.5 (—) and 1.5 (—), for the period between surveys 6 and 7. (b) Estimated proportions of subjects experiencing some disease progression for non-smokers with mean calculus indices 0 (—) and 1 (—), and proportions of subjects experiencing some disease regression for non-smokers with mean gingival indices 0.5 (—) and 1.5 (—), during the period between surveys 6 and 7.

those participating in this study. In this sense, the patient cohort followed for 26 years in the present study represents a uniquely maintained middle-class male population of Caucasian ethnicity. Hence, it is reasonable to expect that disease progression would be scarce in this cohort. Indeed, only two of the subjects with contiguous examinations ( $n = 380$ ) progressed from Level 1 to Level 2 using the 5th European Workshop on Periodontology definitions of disease and had advanced LoA at multiple sites at the last examination in 1995.

In order to evaluate the factors influencing disease progression to initial periodontitis, data on transitions from Level 0, i.e. zero LoA with at the most one inter-proximal site with LoA  $\geq 3$  mm, to Level 1, i.e. some periodontal lesions including the presence of proximal attachment loss of  $\geq 3$  mm in  $\geq 2$  non-adjacent teeth, were analysed.

The definitions of Levels 0, 1 or 2 patients may be open to debate. At the

5th European Workshop on Periodontology in 2005, the proposed criteria for a two-level definition of a ‘‘periodontal case’’ were discussed at length. Deliberately, the Level 1 definition represents a sensitive case definition representing an initial stage of periodontitis, and the Level 2 definition allows a more specific case definition for patients with substantial extent and severity of periodontitis. The proposed criteria were recommended for the identification of risk factors (Tonetti & Claffey 2005). In the light of the dentally aware and well-maintained male population of the present study, it seemed entirely reasonable to apply the Level 1 case definition for the modelling process when using the ante-dependent Markov chain model.

At all examinations, LoA was assessed relative to probing depth to the CEJ. Hence, LoA was the primary determinant of disease progression. Probing depths were available in examination 3 in 1973 and thereafter when recession was specifically addressed. It is obvious that probing depth reflects the severity of the disease, while LoA may be a more definite assessment of past disease.

Because both the assessment of LoA and the probing depth depend on the penetration of a periodontal probe following an applied force, it is recognized that these variables yield multiple sources of error (Mombelli 2005). It is crucial that the dimensions and the applied forces are standardized and controlled (Mombelli et al. 1992, 1997). Angulation of the probe and its incremental markings may also lead to variability during assessment. Last, but not least, the conditions of the gingival tissues (healthy *versus* inflamed) have a profound effect on the penetration depth of the probe (Armitage et al. 1977, Fowler et al. 1982). As spontaneous healing of periodontal lesions with histological gain of attachment is unlikely to occur (Caton et al. 1980), it is logical to assume that regression to Level 0 may be due to resolution of the inflammation rather than to true attachment gain, although the latter cannot be excluded completely.

Generally, the presence of  $\geq 2$  teeth with LoA of 3 mm or more over time is a definition applied to express disease progression (Tonetti & Claffey 2005). The threshold of two teeth is set to minimize the risk of including cases of progression arising due to reasons other than periodontitis. The threshold of a longitudinal

LoA of 3 mm or more over time is based on evidence extensively documented in the periodontal literature.

An increasing rate of disease progression and a decreasing rate of disease regression during the course of the study might have been expected due to the fact that the subjects were getting older. The decrease in the rate of disease progression that was apparent after survey 4 was therefore rather unexpected (although there were subsequent increases after surveys 5 and 6) and may be due to an initial improvement in the subjects’ dental care as a consequence of their taking part in the study, although this can only be a conjecture.

A higher mean CI substantially influenced the progression of disease, irrespective of the smoking status. A higher mean CI resulted in net disease progression occurring some 7–8 years earlier than that for a low mean CI. This points to the importance of calculus as a plaque-retaining and -promoting factor (Waerhaug 1956), the regular removal of which appears to be of utmost importance even in this dentally aware and well-maintained patient cohort.

It is interesting to note that increasing Calculus rather than PII were predictive for progression of disease. This highlights the difficulty in evaluating subgingival plaque as well as accumulation of supra-gingival plaque on the teeth in longitudinal studies, where the intervals between observations are too long to enable a precise representation of the oral hygiene status of the dentition over time. Obviously, the assessment of the calcified plaque indirectly reflected the amount of deposits in a more reliable way.

The results of the present analysis also showed that, in this Norwegian population, smoking led to a doubling of the rate of disease progression, with net disease progression (i.e. the rate of progression exceeding the rate of regression) occurring some 3–4 years earlier compared with that in the non-smokers.

Increasing mean GI significantly increased the rate of regression of disease by a factor of approximately 5 (for a unit increase). This is an interesting finding that may indicate that the inflammatory response of the gingiva affected the healing process rather than the disease progression rate and hence maintained the lesions in a state of homeostasis. Those patients (e.g. smokers) who do not have a strong inflammatory response to plaque may represent a susceptible population. This

is supported by the findings of the present study. However, for over 50 year olds, there seems to be little disease regression whatever the value of GI. In the early stages of the disease process, i.e. in the transition from health/gingivitis to initial/early periodontitis, the apparent loss and gain of attachment is likely to reflect a dynamic process that in turn reflects the homeostatic mechanisms of inflammation in response to the presence of dental plaque. It is only at older ages that these fail and disease progresses. In subjects without inflammation, the clinical situation appears to present with LoA several years earlier.

This agrees with the previous analysis of these data (Schätzle et al. 2003b), which demonstrated that the effect of gingivitis was in the over 40 year olds and as they approached 60 years of age.

Age and smoking status were the two systemic variables influencing disease progression and regression. It has to be kept in mind that in the present study, the self-reported smoking habits included the consumption of as little as two cigarettes per day. Increasing age lowered the rate of disease regression, while smoking increased the rate of disease progression. In contrast to previous studies (Bergström 2006), the analysis of the present study has used longitudinal data to elucidate the role of these covariates in predicting initial periodontitis.

In a previous study on the natural history of periodontal disease of a shorter duration, with more frequent examinations and shorter intervals between examinations (Faddy et al. 2000), smoking was recognized as having a significant negative effect on disease regression, a phenomenon that could not be detected in the present study, possibly due to the extended periods between examinations varying from 2 to 7 years.

From a clinical point of view, applying a Markov chain ante-dependence model to this 26-year longitudinal study of dentally aware and well-maintained Norwegian males has identified three major factors, calculus, smoking and age, affecting the transition from zero LoA to initial periodontitis. Increased mean CI and smoking were significant predictors of disease progression.

Further, gingivitis and age influenced the regression from initial periodontitis back to health. An increased mean GI increased the regression rate from initial disease back to level zero, while increased age had the opposite effect.

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**Clinical Relevance**

*Scientific rationale for the study:* Because cross-sectional studies cannot identify factors influencing initiation, progression and regression of disease, ante-dependence modelling using a Markov chain has allowed the results of a sequence of periodontal examinations to be analysed longitudinally to describe temporal changes in patients' levels of disease.

*Principal findings:* In analysing the parameters of a 26-year longitudinal cohort with seven consecutive examinations, the ante-dependence modelling revealed increasing mean CI and smoking as significant predictive factors for initiation of chronic periodontitis, while increasing mean GI and lower age were associated with regression of initial periodontitis back to a healthy state.

*Practical implications:* In a middle-class, dentally aware cohort like the Norwegian males in this study, increased calculus deposits and smoking were the determining factors for progression from health to initial periodontitis as defined by the 5th European Workshop on Periodontology, while older age increased the likelihood of periodontitis persistence.