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Analytical epidemiology of periodontitis

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Abstract

Aims: To review the literature related to the analytical epidemiology of periodontitis generated over the past decade. This review does not deal with descriptive epidemiologic studies of the prevalence, extent and severity of periodontitis with respect to global geography, but focuses exclusively on analytical epidemiology issues, including the challenges posed by the use of different case definitions across studies, current theories and models of disease progression, and risk factors associated with the onset and progression of periodontitis.

Methods: Relevant publications in the English language were identified after Medline and PubMed database searches.

Findings and conclusions: There is a conspicuous lack of uniformity in the definition of periodontitis used in epidemiologic studies, and findings from different research groups are not readily interpretable. There is a lack of studies that specifically address the distinction between factors responsible for the onset of periodontitis *versus* those affecting its progression. Colonization by specific bacteria at high levels, smoking, and poorly controlled diabetes have been established as risk factors for periodontitis, while a number of putative factors, including specific gene polymorphisms, have been identified in association studies. There is a clear need for longitudinal prospective studies that address hypotheses emerging from the cross-sectional data and include established risk factors as covariates along with new exposures of interest. Intervention studies, fulfilling the ''targeting'' step of the risk assessment process, are particularly warranted. Obvious candidates in this context are studies of the efficacy of elimination of specific bacterial species and of smoking cessation interventions as an alternative to the traditional broad anti-plaque approach in the prevention and control of periodontitis. Ideally, such studies should have a randomized-controlled trial design.

Key words: epidemiology; periodontitis; periodontal disease; risk factors

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This review examines recent literature related to the analytical epidemiology of periodontitis. As both the 1st European Workshop in Periodontology from 1993 and the latest World Workshop in Periodontics from 1996 did include chapters related to the epidemiology of the periodontal diseases (Papapanou 1994, 1996), the present text examines the literature published over the last decade, i.e., since 1994. The review does not deal with any descriptive epidemiologic studies of periodontitis such as those reporting differences in prevalence, extent, and severity with respect to global geography. Instead, it focuses exclusively on analytical epidemiology issues including the challenges posed by the use of different case definitions across studies, current theories and models of disease progression, and risk factors associated with the onset and progression of periodontitis. The literature review was carried out as follows: Medline and PubMed databases were used to search for the following key words: ''periodontal disease'', ''periodontitis'', ''disease progression'', ''disease onset'', ''risk factor'', ''epidemiology'', and ''case definition''. Each of these searches was exploded, combined to that of ''periodontal disease'' and ''periodontitis'', and finally limited to the period from 1994 to present. Articles published in language other than English were excluded, and the identified references were saved into a reference manager software. All citations and their abstracts, whenever available, were printed and screened to determine articles to be obtained, evaluated, and finally included in the review. In addition to the Medline and PubMed searches, selected references quoted in a number of articles were evaluated and, whenever appropriate, included in the review, according to their relevance to the theme in question. Citations related to risk factors were organized in two tables according to their study design (cross-sectional/longitudinal) and sorted

in chronological order. However, the studies included in these tables are not intented to be exhaustive of all published work.

Case Definition of Periodontitis in Epidemiologic Studies

The definition of the specific outcome under investigation is essential in all epidemiologic studies. However, the global periodontal literature has been plagued by a plethora of case definitions of periodontal disease. Studies have used an array of clinical signs and symptoms such as gingivitis, bleeding on probing (BoP), pocket depth (PD), clinical attachment loss (CAL), as well as radiographically assessed alveolar bone loss (Beck et al. 1990, Machtei et al. 1992, Locker & Leake 1993). Because of inconsistencies in the use of the above disease indicators, large variations in the definition of periodontitis are inevitable. In addition, combinations of disease indicators, such as PD and CAL at specific levels (Beck et al. 1990, Machtei et al. 1992), have also been used under the rationale that they represent both cumulative tissue destruction (CAL) and current pathology (PD) (Burt & Eklund 1999, Arbes et al. 2001). To further complicate the issue, there is a wide variation in the threshold values used in the definition of a ''case'', regardless of the indicators used, as well as in the definitions of incident or progressive disease. Finally, studies have also used tooth loss – the ultimate end point of periodontitis – as an additional outcome variable in the context of risk assessment (Krall et al. 1994, 1997, Machtei et al. 1999, Chen et al. 2001). As is evident by the studies presented in Tables 1 and 2, these inconsistencies in the case definition affect both the current and progressive disease distribution estimates in the population and the estimates of odds ratio and relative risk and, consequently, render the comparison between study findings a true challenge. Consequently, although several studies are focused on the role of the same risk factors, a direct comparison of odds ratio or relative risk between studies is hard. Another issue that needs to be accounted for in terms of case definitions is the use of full- or partial-mouth recording of parameters such as CAL and/or PD. National, large-scale epidemiologic studies have usually used partial-mouth recording methodologies, such as the system used in National Health and Nutrition Examination Survey (NHANES) III study, which examined only two sites (mesiobuccal and midfacial) in two randomly selected quadrants under the assumption that these measurements are representative of the full-mouth status (Albandar et al. 1999, Albandar & Kingman 1999). In contrast, smaller scale studies are more likely to have used full-mouth examination methodologies (Beck & Koch 1994, Beck et al. 1995, Elter et al. 1999). Several studies have documented that the use of partial-mouth examinations usually leads to an underestimation of both the prevalence and the severity of the disease (Hunt 1987, Kingman et al. 1988, Hunt & Fann 1991, Kingman & Albandar 2002), which, in combination with the lack of a uniform case definition of periodontitis, has an inevitable effect on inferences related to risk and prognostic factors (Kingman et al. 1991, Beck 1994). For the above reasons, it appears that a consensus decision on the adoption of uniform criteria for both prevalent and incident periodontitis is essential in order to advance analytical epidemiological research of periodontitis in the future.

Disease Progression

In the mid-1980s, investigators at the Forsyth Institute (Socransky et al. 1984) introduced a theoretical model to describe the nature of the progression of periodontal disease, collectively referred to as the ''random burst theory''. According to this theory, periodontal tissue support is lost during short, acute episodes of disease activity (''bursts''), followed by prolonged periods of quiescence. Thus, the loss of attachment recorded by sequential probing assessments is thought to reflect the cumulative effect of such repeated episodes. Since then, a number of publications have re-visited the issue of linear *versus* episodic disease progression (Reddy & Jeffcoat 1993, Breen et al. 1999a, b, Gilthorpe et al. 2003). In this context, it must also be realized that, as long as disease progression is measured by linear measurements of vertical attachment loss along the root surface, ''bursts'' of activity will be the de facto favoured alternative, because the magnitude of the detectable progression is directly dependent on the incremental readings of the periodontal probe. In a meta-analysis of studies published prior to 1997, Breen et al. (1999a) concluded that, because of considerable differences in the design of follow-up studies (duration, number of subjects and sites examined, number of serial probing assessments, probe designs, progression thresholds employed, etc.), valid comparisons between the studies are generally not possible. These authors also noted that the majority of the publications report only on sites that experience loss of attachment, with little or no reference to sites that experience gain of attachment or even a cyclical progression pattern, i.e., sequential exacerbation, remission, and repair. In a longitudinal study of 16 subjects with moderate-to-severe periodontitis who were probed on four occasions over 6 months, the same research group (Breen et al. 1999b) explored the ability of a specific analytical method (option-4 algorithm) to reduce measurement error and improve the accuracy and sensitivity of site-specific attachment level changes. Over the observation period, bi-directional attachment-level changes were detected in this particular study in all subjects and at approximately half of the monitored sites. In a follow-up of 44 patients with untreated periodontitis monitored over 18 months, Reddy & Jeffcoat (1993) used an electronic, controlled-force periodontal probe and digital subtraction radiography to detect the pattern of attachment loss and bone loss, respectively, and reported that (i) the majority of the sites displayed no discernible change, while (ii) 23% of the sites lost and 5% gained periodontal tissue support. Finally, Gilthorpe et al. (2003) confirmed the cyclical nature of periodontal disease progression using multilevel modelling, and proposed that the ''linear'' and ''burst'' theories of periodontal disease progression are a manifestation of essentially the same phenomenon, i.e., of the sequential deterioration and repair that occur at the individual tooth sites over time.

Risk Factors for Periodontitis

In general, there is reasonable consistency in the recent literature pertaining to the identification of risk factors for periodontitis. As stated by Beck et al. (1995), ''risk factors can be defined as characteristics of the person or environment that, when present, directly result

Table 1. Cross-sectional and case–control studies

Study	Aim/methods	Outcome(s)	Exposure(s)	Results
Grossi et al. (1994)	To identify risk indicators and putative risk factors for periodontitis Cross-sectional study (US – Erie County, NY): $N = 1426$ adults aged 25–74 years. Mostly whites (90.3%)	Mean CAL and classification as: healthy ($\leqslant 1$ mm CAL); low (>1 and $\geqslant 2$ mm); moderate (>2 and $\leqslant 3$ mm); high (>3 but $\leqslant 4$ mm); and severe ($\geqslant 4$ mm)	Periodontal status: supragingival plaque, GB, subgingival calculus, PD, CAL. Subgingival microbiota: *Actinobacillus actinomycetemcomitans*, *Tanerella forsythensis*, *Campylobacter rectus*, *E. saburreum*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *capnocytophaga* spp. and *Prevotella intermedia*. Other covariates: age, gender, race, education, income, smoking and numbers of packs/year, exposure to occupational hazards, systemic diseases	In a multivariable logistic model, age (ORs ranging from 1.72 for age group 35–44 to 9.01 for age group 65–74), male gender (OR = 1.36; 95% CI: 1.06–1.76), smoking (ORs ranging from 2.05 [95% CI: 1.47–2.87] for light smokers to 4.75 [95% CI: 3.28–6.91] for heavy smokers), diabetes (OR = 2.32; 95% CI: 1.17–4.60), *P. gingivalis* (OR = 1.59; 95% CI: 1.11–2.25) and *T. forsythensis* (OR = 2.45; 95% CI: 1.87–3.24) were positively associated with severity of CAL, while *capnocytophaga* spp. (OR = 0.60; 95% CI: 0.43–0.84), anaemia (OR = 0.65; 95% CI: 0.42–0.99), allergy (OR = 0.77; 95% CI: 0.58–1.00) and education (OR = 0.65; 95% CI: 0.51–0.85) were protective against severe CAL
Grossi et al. (1995)	To identify factors associated with alveolar BL. Cross-sectional study (US – Erie County, NY): $N = 1361$ aged 25–74 years. Mostly whites	Radiographic alveolar BL: distance from CEJ to the alveolar crest. Inter-proximal BL: healthy (0.4, <2 mm), low (2.0, <3.0 mm), moderate (3.0, <4.0 mm), and severe ($\geqslant 4.0$ mm)	Supragingival plaque, GB, subgingival calculus, PD, CAL. *A. actinomycetemcomitans, T. forsythensis*, *C. rectus*, *Eubacterium saburreum*, *F. nucleatum*, *P. gingivalis, capnocytophaga* spp., and *P. intermedia*. Other covariates: age, gender, race, education, income, smoking, and packyears, exposure to occupational hazards, systemic diseases	In a multivariable logistic regression model, age (ORs ranging from 2.6 [95% CI: 1.75–3.83] for age group 35–44 to 24.08 [95% CI: 15.93–36.29] for age group 65–74), male gender (OR = 1.29; 95% CI: 1.05–1.61), race other than white (OR = 2.40; 95% CI: 1.21–4.79), smoking (ORs ranging from 1.48 [95% CI: 1.02–2.14] for light smokers to 7.28 [95% CI: 5.09–10.31] for heavy smokers), *P. gingivalis* (OR = 1.73; 95% CI: 1.27–2.37), *T. forsythensis* (OR = 2.52; 95% CI: 1.98–3.17), were significantly associated with increasing severity of BL, while kidney disease (OR = 0.55; 95% CI: 0.35–0.85), allergy (OR = 0.76; 95% CI: 0.59–0.98) and education (OR = 0.67; 95% CI: 0.53–0.98), significantly decreased the severity of BL.
Martinez Canut et al. (1995)	To evaluate the influence of tobacco on the severity of periodontal disease and to quantify the strength of the influence in relation to the amount of tobacco consumed. Cross-sectional study (Spain): $N = 889$ subjects with mild and advanced periodontitis, including 52.6% smokers	GR, PD, CAL, and tooth mobility	Smoking status (yes/no), and categorization based on daily cigarette consumption. Other covariates: age, sex	Daily cigarette consumption had a dose–response effect on GR, PD, CAL, and mobility. The effect of age and tobacco on mobility was comparable for adults older than 51 years of age and consuming more than 21 cigarettes/day (0.76 and 0.82, respectively). Tobacco consumption had a dose–response effect on CAL across all ages
Bridges et al. (1996)	To determine differences in plaque and gingival indices, bleeding scores, PDs, loss of attachment, and number of missing teeth between diabetic and non-diabetic subjects. Case–control study (US): $N = 233$ men aged 24–78 years. One hundred	PI, GI, bleeding on probing, PD, CAL, and number of missing teeth	Diabetes mellitus Type 1 and Type 2. Glycosylated haemoglobin, fasting blood glucose, serum insulin, and C-peptide levels. Covariates: age, income, education, brushing, flossing, dental care, smoking status	PI ($p<0.0001$); GI ($p<0.0002$); bleeding score ($p<0.0001$); PD ($p = 0.0059$); loss of attachment ($p<0.0001$); and missing teeth ($p<0.005$) were significantly higher in diabetic than non-diabetic men. Income and education were negatively associated with periodontal status (plaque, gingival indices,

	and eighteen diabetic (46 type 1 and 72 type 2) and 115 non-diabetic subjects, matched for age and BMI			and missing teeth with income; and plaque and gingival indices, PD, CAL, and missing teeth for education) for both diabetic and non-diabetic men
Alpagot et al. (1996)	To evaluate risk indicators of periodontal disease. Cross-sectional study (US): $N = 117$ subjects 18 years and older.	Healthy sites: GI = 0, PD $\leqslant$3 mm and CAL $\leqslant$1 mm; gingivitis sites: GI > 0, PD $\leqslant$3 mm and CAL $\leqslant$2 mm; periodontitis sites: GI > 0, PD > 3 mm and CAL > +3 mm. Subjects were assigned to periodontitis and gingivitis groups based on the subject's most DS per sextant	GCF, plaque, βG, NE, MPO, *F. nucleatum*, *P. intermedia*, and *P. gingivalis*. Other covariates: age, race (white, black, native American, and Asian), cigarette smoking (pack/years).	*F. nucleatum*, *P. gingivalis*, and *P. intermedia* were associated with PD and CAL. Age, race, smoking pack/years, βG, NE, MPO, *F. nucleatum*, *P. gingivalis*, and *P. intermedia* were risk indicators for periodontitis in this racially diverse urban population
Kornman et al. (1997)	To investigate the association of a specific polymorphism in the IL-1 gene cluster and the severity of periodontitis. Case–control study (US): $N = 134$ aged 35 and older whites only.	Periodontitis: mild ($n = 49$): no PD 3+ mm and no sites with BL > 15% of the root length. Moderate ($n = 42$): <4 inter-proximal sites with $\geqslant$50% BL and a total mean BL of 17–28%; Severe ($n = 43$): $\geqslant$7 inter-proximal sites with $\geqslant$50% BL and total mean BL of >34%.	SNPs at the following positions: IL-1A(−889); IL-1B (−511); IL-1B (+3953); IL-1RN (intron 2) and TNF-A −308. Other covariates: smoking (current or not)	Among non-smokers, there was a strong association between severity of periodontitis and the composite genotype comprising allele 2 at position IL-1A −889 plus allele 2 at position +3953 of the IL-1B gene (OR 6.8; 95% CI: 1.01–45.62). In non-smokers aged 40–60 years, the composite genotype was present in 78% of the subjects with severe ($n = 9$), 26% of those with moderate ($n = 30$), and 16% of those mild BL ($n = 32$) (OR 18.9; 95% CI: 1.04–343.05).
Gore et al. (1998)	To determine the distribution of specific polymorphisms in the IL-1 gene cluster in patients with adult periodontitis and their matched controls; and to examine possible association of genotype with cytokine production by oral and peripheral blood PMN. Case–control study (US): $N = 64$ (32 cases and 32 age- and sex-matched 32 controls) white	Periodontal disease: early ($n = 10$); moderate ($n = 10$); and advanced ($n = 12$)	SNPs at the following positions: IL-1B +3953, IL-1B −511, IL-1A −889, IL-1RN, assessed at oral and peripheral blood PMN. Smoking status of controls was not determined.	Homo- and heterozygocity with the rare allele 2 at position IL-1B+3953 (1/2 and 2/2) was significantly more frequent among cases with advanced adult periodontitis than among early and moderate periodontitis. Peripheral blood PMNs of these patients produced increased levels of the IL-1β compared with patients without allele 2, although this increase was not statistically significant. The composite genotype (IL-1B +3953 allele 2 and IL-1A −889 allele 2) was carried by 50% of cases with advanced periodontitis, 25% of cases with early/moderate periodontitis, and 28% of controls. However, this difference did not reach statistical significance
Boström et al. (1998a)	To evaluate the influence of smoking on TNF-α levels in GCF of patients with untreated moderate-to-severe periodontal disease (30 current smokers, 19 former smokers, and 29 non-smokers, 31–79 years old). Cross-sectional study (Sweden): $N = 78$	TNF-α in GCF	Smoking status: current (mean 19.3 cigarettes/day for an average of 25.4 years), former (19.5 cigarettes/day for17 years) and never. PI, GB, mean PD. Sites with PD$\geqslant$4 mm were defined as DSs and were expressed as percentage. Other covariates: age, gender, and presence in dental plaque of *A. actinomycetemcomitans*, *P. gingivalis*, *intermedia*	TNF-α levels were significantly higher in former and current smokers when compared with never smokers. TNF-α (log) was associated with current and former smoking status and PI after adjusting for GB and DS
Boström et al. (1999)	To examine the influence of tobacco smoking on GCF levels of IL-6, IgA, IgG, and TNF-α in patients	IL-6, IgA, IgG, and TNF-α in GCF	Current (42%, mean 21 cigarettes/day for 24 years), former (26%, mean 20 cigarettes/day for 18 years), and never	GCF IL-6 was not associated with smoking. Levels of TNF-α were significantly higher among smokers when compared with non-smokers. The ratio of

Table 1. (Contd.)

Study	Aim/methods	Outcome(s)	Exposure(s)	Results
	with moderate-to-severe periodontal disease. Cross-sectional study (Sweden): $N = 108$, age range 30–81 years		smokers (32%). PL, GB, PD. Other covariates: presence in dental plaque of *A. actinomycetemcomitans*, *P. gingivalis*, and *P. intermedia*	TNF-α/albumin was statistically greater in current smokers as compared with non-smokers. IgA/IgG and IgA/albumin were found to be correlated in all subjects. There was no significant difference in the level of the investigated pathogens across smoking groups
Galbraith et al. (1999)	To examine the distribution of SNPs at the IL-1B +3953 and TNF-A −308 in adults varying levels of periodontal disease; and to examine the influence of the genotype on cytokine production by oral and peripheral blood PMNs. Cross-sectional study (US): $N = 85$ (20 with advanced periodontitis, 20 with plaque-associated gingivitis, and 45 referent subjects). Whites, aged 35–65 years old	Advanced periodontal disease: ⩾3 sites with PD⩾7 mm and CAL > 5 mm. Oral and peripheral blood PMN IL-1β and TNF-α	SNPs at IL-1B +3953 and TNF-A −308. Bleeding, mobility, smoking	Homo- and heterozygocity for the rare IL-1B +3953 allele 2 (1,2 and 2,2) was significantly elevated in the patient group compared with the referent group. TNF-A −308 1,1 genotype was significantly elevated in patients with advanced periodontitis compared with those with gingivitis. Allele 1 frequency was higher in patients with gingivitis and advanced periodontitis compared with the referent group. No significant differences were found in IL-1β production by LPS-stimulated peripheral blood PMNs, or in TNF-α synthesis by either oral or peripheral blood PMNs. Increased IL-1β production by oral PMNs was observed in carriers of allele 2 with advanced periodontal disease.
Genco et al. (1999)	To investigate the relationship of periodontal disease to stress, distress, and coping behaviours in a large population-based sample of adults. Cross-sectional study (US): $N = 1426$ aged 25–74 years. Whites (95.6%)	Periodontal status was categorized by mean CAL as healthy (0–1 mm), low-level disease (1.1–2), moderate (2.1–3), high (3.3–4) and severe (4.1–8); and by mean ACH as healthy (0.4–1.9 mm), low-level disease (2–2.9), moderate (3–3.9), and severe (⩾4).	Life Event Scale, measures of chronic stress (Problems of Everyday Living Scale), measures of distress, coping styles and strategies, and hassles and uplifts. Other covariates; age, gender, years of education, smoking, income, diabetes, allergy, anaemia. *A. actinomycetemcomitans*, *T. forsythensis*, *C. rectus,* *Capnocytophaga* species, *E. saburreum*, *F. nucleatum*, *P. gingivalis*, and *P. intermedia*	Subjects with high emotion-focused coping and more financial strain were twice as likely to have more severe CAL (OR: 2.24; 95% CI: 1.15–4.38) and ACH (OR: 1.91; 95% CI: 1.15–3.17) than those with less financial strain. Similar patterns were observed for low problem-focused copers (CAL: OR = 2.21; 95% CI: 1.11–4.38; and ACH: OR = 2.12; 95% CI: 1.28–3.51). The risk for periodontal disease as measured by CAL and ACH was higher in subjects with high financial strain and high emotion-focused coping (poor coping). High financial strain accompanied by high levels of problem-focused coping (good coping) entailed no risk for periodontitis
McDevitt et al. (2000)	To evaluate the association between the IL-1 gene polymorphism in a broad spectrum of patients typically found in a dental practice. Case–control study (US): $N = 90$ (44 cases and 46 controls) adults 35 years and older	Periodontal status: mean inter-proximal BL. Cases: BL⩾3.0 mm or at least 10 teeth with at least 1 site with ⩾3.0 mm BL and at least 2 sites in each quadrant with ⩾3.0 mm BL. Controls: no more than 2 sites with BL⩾3.0 mm	SNPs at positions IL-1A +4845, IL-1B +3954. Other covariates: age, gender, ancestry, smoking status	Patients with moderate-to-severe periodontal disease were more likely (41%) to be IL-1 genotype positive according to Kornman et al. (1997) compared with patients in the healthy and mild group (28%), but the difference did not reach statistical significance. Age (OR = 1.26, $p < 0.001$), smoking history (OR = 7.43, $p = 0.031$) and being IL-1 genotype positive (OR = 3.75) were significantly associated with severity of periodontal disease. There was a significant interaction between smoking history and positive IL-1 genotype

				(OR = 1.68, $p = 0.045$). In a separate analysis conducted for patients of European origin, the OR for those IL-1 genotype positive was stronger (OR = 5.27, $p = 0.026$) than that observed for the total population
Parkhill et al. (2000)	To explore the association of IL-1 gene polymorphisms with EOP. Case–control (UK): $N = 70$ with EOP (including 21 with localized EOP) and 72 without clinical evidence of periodontitis Caucasians	EOP: clinical and radiographic evidence of rapid rate of tissue destruction with age of onset <35 years. L-EOP: $\geqslant 3$ mm of BL confined only to incisors and first molars and adjacent tooth surfaces. Controls: CAL $\leqslant 1$ mm	SNPs at positions IL-1B +3953 and IL-1RA. Smoking	When compared with the control group, subjects with EOP were 2.22 more likely to carry the IL-1B +3953 1/1 genotype. There was a significant difference in the IL-1B +3953 allele distribution between EOP smokers and control smokers. There was no difference in the frequency of IL-1RA allele occurrence or genotype between EOP and control smokers, or EOP and control non-smokers
Bergström et al. (2000b)	To examine the association of pocket depth and alveolar bone height with smoking. Cross-sectional study 1992–1993 (Sweden): $N = 244$ aged 20–69 years	Pocket depth $\geqslant 4$ mm defined a DS and $\geqslant 6$ mm a severely DS. GB and PI. Periodontal bone height was calculated as a mean across all measured inter-proximal sites	Smoking exposure was defined in terms of consumption (number of cigarettes/day), duration (number of years of smoking), and lifetime exposure (Product of daily consumption, and years of duration-cigarette/years). Heavy *versus* light consumption: $\geqslant 10$ cigarettes/day *versus* <10 cigarettes/day Duration: $\geqslant 15$ years *versus* <15 years Life-time exposure: $\geqslant 200$ cigarette/years *versus* <200 cigarette/years. Other covariates: age	Compared with former and non-smokers, current smokers had the highest prevalence of DSs ($\geqslant 4$ mm) with older (40–69) current smokers (27.0%) having a significantly higher prevalence than younger (20–39) current smokers (3.8%). This pattern was observed when comparing heavy *versus* light smokers according to consumption, duration, and lifetime exposure. In terms of periodontal bone height, there was no difference among current, former and non-smokers in the younger group (20–39). However, in the older group (40–69), current smokers had lower bone height than non-smokers. In multiple regression, life-time exposure ($p<0.001$) was associated with the frequency of DSs and periodontal bone height after adjusting for age, GB, and PI
Armitage et al. (2000)	To examine the association between the composite genotype of IL-1A +4845 and IL-1A +3954 (formerly +3953) and the severity of periodontal disease in a population of Chinese heritage. Cross-sectional study (US): $N = 300$, 21–69 years old	PI, bleeding on probing, PD, CAL and GR. Healthy or gingivitis: mean CAL $\leqslant 0.5$ and no inter-proximal sites with CAL $\geqslant 3$ mm. Initial: mean CAL $\geqslant 0.6$–1.5 mm, no inter-proximal sites with CAL $\geqslant 3$ mm; Moderate: mean CAL = 1.6–2.4 mm and $\leqslant 8$ sites with inter-proximal CAL $\geqslant 3$ mm distributed through at least three quadrants or at least 6 teeth; Severe: mean CAL $\geqslant 2.5$ and $\geqslant 1$ site with CAL $\geqslant 5$ mm in three out of four quadrants	SNPs at positions IL-1A +4845 and IL-1A +3954. Other covariates: age, gender, ethnicity, smoking status: current, former and never cigarette consumption: pack/day $\times$ number of years	The composite genotype according to Parkhill et al. (2000) was present in 2.3% (7/300) of the subjects. Allele 2 at position IL-1A +4845 was carried by 17% of the population, of whom only two were homozygous. Allele 2 of IL-1B +3954 was carried by only 3.3% of the study population and all subjects were heterozygous
Boström et al. (2000)	To examine the influence of smoking on the GCF levels of IL-1β and IL-1ra in a population of patients with established periodontitis. Levels of IgA and IgG in GCF were also determined. Cross-sectional study (Sweden): $N = 40$ aged 32–86 years	PL, GB, PPDall, DS, PPDds. DSs: sites with PD $\geqslant 4$ mm PPDall: mean across all sites with PD. PPDds: mean PD of DSs	Smoking status: current (20 cigarettes/day for and average of 31 years), former, and non-smokers. Other covariates: age and gender. GCF: IL-1β, IL-1ra, IgA, IgG, albumin, protein	Neither IL-1β nor IL-1ra was significantly different in smokers and non-smokers. The same was the case for IgA, IgG, albumin, and protein. IL-1β and IL-1ra were correlated among smokers. IL-1β was correlated with albumin and protein in smokers and non-smokers. Correlations among smokers and non-smokers were found between IgA and IgG; IgA and albumin; IgG and albumin; IgA and protein and IgG

Table 1. (Contd.)

Study	Aim/methods	Outcome(s)	Exposure(s)	Results
				and protein. However, these correlations were not different between smokers and non-smokers.
Albandar et al. (2000)	To examine whether the association between cigar and pipe smoking and periodontal disease is similar to the one observed with cigarette smoking; and whether cigar, pipe, and cigarette smoking are associated with tooth loss. Cross-sectional study (USA): $N = 705$ aged 21–92 years, 52% males and 87% white	Subjects with $\geqslant 8$ teeth or $\geqslant 50\%$ of teeth with GB were classified as having extensive gingival inflammation; those with 3–7 teeth or 25–49% of their teeth as with limited gingival inflammation. Periodontitis: advanced: PD $\geqslant 5$ mm in 4+ teeth (or $\geqslant 30\%$ of teeth), or PD $\geqslant 4$ mm in 8+ teeth (or $\geqslant 60\%$ of teeth); moderate: PD $\geqslant 5$ mm in 2–3 teeth or PD $\geqslant 4$ mm in 4–7 teeth (or 30–59% of teeth); mild: PD $\geqslant 4$ mm in 1+ teeth or PD $\geqslant 3$ mm in 2+ teeth	Cigar, pipe and cigarette smoking: current, former, and never. Other covariates: age, gender, and race	Current cigarette smokers exhibited the worst periodontal status followed by former smokers. Current (25.7%) and former (20.2%) cigarette smokers had higher prevalence of moderate/advanced periodontitis than non-smokers (13.1%). However, current cigarette smokers had lower GB than non-smokers (6.6% *versus* 17.9%, $p < 0.08$). Former cigarette smokers (13.6%) also had lower GB than non-smokers. Calculus was more prevalent among current cigarette smokers. Current or former pipe or cigar smokers had poorer periodontal conditions than non-smokers as indicated by higher prevalence of moderate/advanced periodontitis (17.6% *versus* 6.1%, $p < 0.006$). As with cigarette smoking, current or former pipe and cigar smokers had lower prevalence of GB (8% *versus* 15.7%) but lower subgingival calculus. In multiple linear regression, current and former smoking, regardless of type, was associated with increased percentage of subjects with moderate/advanced periodontitis after adjusting for age, gender, race, and numbers of years of being smoking cigarette, cigar and pipe. Current smoking was also associated with higher number of missing teeth
Boström et al. (2001)	To describe the detection rates of selected bacterial species and analyse their inter-relationships in smokers and non-smokers. Case–control study convenience sample (Sweden): $N = 64$ aged 36–86 years. 33 smokers and 31 non-smokers	Subgingival *P. gingivalis*, *P. intermedia*, *Prevotella nigrescens*, *T. forsythensis*, *A. actinomycetemcomitans*, *F. nucleatum*, *Treponella denticola*, *Peptostreptococcus micros*, *C. rectus*, *Eikenella corrodens*, *Selenomonas noxia* and *Streptococcus intermedius*. Checkerboard hybridizations non-colonized *versus* colonized. Non-colonized and less heavily colonized *versus* heavily	PD (mean score for 4 sites: buccal, distal, lingual, and mesial). GB (yes/no within 30 sites in response to probing with a pressure of approximately 0.25 N). Other covariates: age and gender	Using score 1 as cutoff for presence, contrasting colonized *versus* non-colonized patients, eight out of 12 species were detected in $\geqslant 90\%$ of both smokers and non-smokers. Using score 4 as cut-off, contrasting heavily colonized patients *versus* non-colonized and less heavily colonized patients, detection rates decreased in both smokers and non-smokers. No significant differences in detection rates were observed between smokers and non-smokers. Logistic regression analysis indicated that neither smoking, PD nor GB influenced the occurrence of the species analysed
Laine et al. (2001)	To investigate the distribution of polymorphisms in the genes of the IL-1 cluster among periodontitis patients and controls after adjusting for selected risk factors. Case–control study Convenience sample (the Netherlands): $N = 105$ (53 cases and 53 controls) aged 25	Cases: severe periodontitis $\geqslant 7$ inter-proximal sites with 50% BL. Controls: subjects with < 4 mm PD and no sites with BL	SNPs at IL-1A +3954, IL-1B and IL-1RN. Smoking (current and never). *A. actinomycetemcomitans* and *P. gingivalis*	There were no significant differences in the carriage of the alleles 1 and 2 between cases and controls regardless of their smoking status. When smokers and non-smokers were divided based on the presence or absence of *A. actinomycetemcomitans* and *P. gingivalis,* non-smoker cases who were negative for *P. gingivalis* were found to carry significantly more often the combination of alleles IL-1A #2 and IL-1RN #2 than controls (32.1%

	years and older. Caucasians			*versus* 11.3%, $p = 0.034$). This was also true for *A. actinomycetemcomitans* negative cases (32.5% *versus* 11.3%, $p = 0.018$). Furthermore, subjects were divided in negative and positive for both *A. actinomycetemcomitans* and *P. gingivalis*. Smoker patients negative for both pathogens were more likely to carry alleles IL-1A #2, IL-1B #2 and IL-1RN #2 than controls (42.1% *versus* 11.3%, $p = 0.0068$).
Papapanou et al. (2001)	To examine the association of the IL-1 gene polymorphism and certain elements of periodontal status. Case–control study (Sweden): $N = 205$ aged >20 years 132 cases and 73 controls age- and gender-matched	Cases: moderate-to-advanced periodontal disease, with several inflamed periodontal pockets, loss of attachment, and radiographic evidence of BL. Controls: no or only minimal CAL despite plaque accumulation and bleeding on probing. Presence of 19 bacterial species subgingivally and levels of serum IgG to these bacteria	SNPs at IL-1A (+4845) and IL-1B (+3954). Age, gender, smoking	The positive polymorphism was more prevalent in cases (26.8%) compared with controls (16.1%) but the difference was not statistically significant ($p = 0.624$). The positive polymorphism was associated with an increase in percentage of sites with AL $\geqslant$ 6 mm (modelled as continuous and discrete) and an overall mean serum antibody response (discrete) in cases. Among non-smokers, the presence of the positive polymorphism was associated with an increase percentage of sites with AL $\geqslant$ 6 mm and mean CAL
Papapanou et al. (2002)	(i) To examine the association of subgingival bacterial profiles to clinical periodontal status in a population with limited access to dental care; (ii) to examine the external validity of the findings from an earlier study (Papapanou et al. 1997). Cross-sectional study (Thailand): $N = 356$, 30–39 and 50–59 years old	PD and CAL were assessed at 6 sites/tooth, at all teeth apart from third molars. Subjects were grouped according to different levels of pocketing/attachment loss: subjects with $\geqslant$3 sites with PD $\geqslant$ 5 mm (59%, G1); $\geqslant$10 sites with CAL $\geqslant$5 mm (50%, G2); and $\geqslant$30 sites with CAL $\geqslant$5 mm (24%, G3)	Subgingival plaque samples were obtained at maximally 14 sites/subject. Checkerboard hybridizations were used to analyse a total of 4343 samples with respect to 27 bacterial species	ORs for heavy colonization (i.e., bacterial levels exceeding the specific thresholds generated in the earlier study by Papapanou et al. (1997) by ''red complex'' species (*P. gingivalis*, *T. forsythensis*, *T. denticola*) were 3.7 (95% CI: 2.3–5.9) for G1; 4.0 (95% CI: 2.5–6.6) for G2; and 4.3 (95% CI: 2.6–7.1) for G3. ORs for heavy colonization by selected ''orange complex'' species (*F. nucleatum*, *P. intermedia*, *P. nigrescens*, *P. micros, E. nodatum*, *C. rectus*, and *Campylobacter showae*) were 1.5 (95% CI: 0.8–2.9) for G1; 1.5 (95% CI: 0.8–2.9) for G2; and 1.5 (95% CI: 0.8–3.1) for G3
Aleksejuniene et al. (2002)	To assess the relationship between psychosocial stress and lifestyle and periodontal status in Lithuanian adults. Cross-sectional study (Lithuania): $N = 681$ aged 35–74	Periodontal disease was assessed by means of the Community Periodontal Index of Treatment Needs (CPITN), including measures of PD and recession	Social support, stress, nervousness, coping, smoking, oral hygiene. Other covariates: age and gender	No association between psychosocial stress and periodontitis. However, lifestyle factors were associated with periodontitis
Meisel et al. (2003)	To examine the role of IL-1 polymorphism as a risk factor for periodontal diseases in a randomly selected population. Interaction between smoking and presence of genotype was also examined. Cross-sectional (Germany): $N = 1085$	Percentage of sites with CAL $\geqslant$ 4 mm: subjects at the upper quintiles were compared with those at the lower quintiles	SNPs at IL-1A (-889) and IL-1B (+3954) Subjects heterozygous and homozygous for the #2 allele at each of the 2 sites analysed were designated as genotype positive. Age, gender, plaque, education, smoking, age at which the subject start smoking, frequency and duration of smoking	Periodontal disease was associated with smokers with positive IL-1 genotype after adjusting for age, sex, education, and plaque (OR = 2.5; 95% CI: 1.21–5.13). There was no association among non-smokers. Smokers had lost more teeth than their non-smoker counterparts regardless of their IL-1 genotype
Al-Zahrani et al. (2003)	To examine the association between obesity and periodontal disease.	Periodontitis defined as at least 1 site with CAL $\geqslant$3 and PD $\geqslant$4	Obesity: BMI and WC. Other covariates: age, race, gender,	A significant association between measures of body fat and periodontitis was found among the younger

Table 1. (Contd.)

Study	Aim/methods	Outcome(s)	Exposure(s)	Results
	Cross-sectional study (US): $N = 13{,}665$ 18+ years of age. Non-Hispanic blacks and whites, Mexican Americans, and others		poverty index, education, time since last dental visit, smoking and diabetes	adults, but not middle-aged or older adults. Adjusted ORs for having periodontitis were 0.21 (0.080–0.565), 1.00 (0.705–1.407), and 1.76 (1.187–2.612) for subjects with BMI < 18.5, 25–29.9, and $\geqslant 30\,kg/m^2$, respectively. Young subjects with high WC had an adjusted OR of 2.27 (1.480–3.487) for periodontitis
Susin et al. (2004)	To estimate the number and percentage of cases with severe attachment loss attributable to cigarette smoking in a representative adult urban population in southern Brazil. Cross-sectional study (Brazil): $N = 974$ aged 30–103 years	Periodontal status: presence of severe attachment loss, defined as subjects with CAL $\geqslant$ 5 mm in $\geqslant$ 30% of the teeth	Smoking status: current and former lifetime consumption (# of cigarettes/day × # of days of habit/20). Smoker: heavy (> 7300 packs); moderate (2735–7300), light (1–2374), and non-smokers (< 1 pack). Other covariates: race (white or non-white), SES, calculus (< 25%, 25–50%, and > 50%)	Nearly half of the population had CAL $\geqslant$ 5 mm at $\geqslant$ 30% of their teeth (49.7%) and had been exposed to cigarette smoking (50.9%). Heavy and moderate smokers had significantly higher prevalence of CAL $\geqslant$ 5 mm than non-smokers. This finding was persistent in multivariate analysis with heavy (OR = 3.6; 95% CI: 2.2–6.0) and moderate smokers (OR = 2.0; 95% CI:1.4–2.9) having higher odds for CAL than non-smokers. The attributable fraction of CAL because of cigarette smoking was 37.7% and 15.6% among heavy and moderate smokers, respectively.

PD, probing depth; CAL, clinical attachment level; OR, odds ratio; CI, confidence interval; BL, bone loss; CEJ, cemento-enamel junction; GR, gingival recession; BMI, body mass index; GI, gingival index; GCF, gingival crevicular fluid; bG, β-glucuronidase; NE, neutrophil elastase; MPO, myeloperoxidase; IL, interleukin; SNP, single nuclear polymorphism; TNF, tumour necrosis factor; PMN, polymorphonuclear cells; PI, plaque index; GB, gingival bleeding; DS, diseased site; IgG, immunoglobulin G; LPS, lipopolysaccharide; ACH, alveolar crestal bone height; EOP, early onset periodontitis; L-EOP, localized EOP; CPITN, . . . ; WC, waist circumference; NHANES, National Health and Nutrition Examination Survey.

in an increased likelihood of a person getting a disease and when absent, directly result in a decreased likelihood''. However, a true distinction between factors affecting the onset of disease (risk factors) *versus* factors affecting the course or progression of pre-existing disease or, further, prognostic factors determining the course of the disease under treatment does not clearly emerge (Beck & Koch 1994, Beck et al. 1995, Elter et al. 1999). This is not a trivial point, and may have profound implications, as exemplified by observations from the medical literature. For example, while there is little dispute that infection with the human immunodeficiency virus (HIV) is causative of the acquired immunodeficiency syndrome (AIDS), it is other factors, such as incident respiratory infections, that may result in the death of the infected patient. Consequently, intervention strategies aimed at prevention of HIV infection will have no impact in the prognosis of an already infected patient, but strategies aimed at preventing respiratory infections clearly will. Both exposures confer risk for, or in this particular case are causative of, specific conditions: the former (HIV infection) of the onset of immunodeficiency, and the latter (respiratory pathogen) of death.

In contrast, a prognostic factor may be any factor that has the capability of predicting the course of a disease under treatment. It may or may not be a true risk factor, and can frequently be an alternative measure of the disease itself. For example, it has been well established both in medical and dental settings that baseline levels of severity of a given disease are associated with treatment outcomes: lymph node involvement and/or presence of metastases can determine cancer prognosis, and the pretreatment severity of the loss of periodontal tissue support is related to the expected outcome of periodontal therapy. However, neither baseline condition can be considered as a ''risk factor''. Instead, both can serve as robust prognostic factors. Undoubtedly, the distinction between risk factors for the onset *versus* progression of a disease, as well as between risk and prognostic factors is a demanding task, as it requires the performance of prospective studies that are specifically designed for this purpose. However, as discussed above, in the field of periodontology, the majority of the studies that are available to the present date are cross-

sectional in nature, have used a plethora of different case definitions and, with single exceptions (e.g., Beck et al. 1995, Baelum et al. 1997), have not addressed this specific issue.

As emerges for the review that follows, the major individual characteristics, clinical conditions, and systemic diseases that have been investigated in epidemiologic studies as putative risk factors for periodontitis include age, gender, race/ethnicity, socioeconomic status (SES), dental plaque, specific subgingival microbiota, cigarette smoking, diabetes mellitus, obesity, HIV infection, osteoporosis, and psychosocial factors. As a preface, we suggest that although several individual characteristics and clinical conditions have been identified as risk factors for periodontitis, a major challenge remains the determination of the time sequence of events that play a role in the disease process, i.e., a verification of ''temporal consistency''. Therefore, a differentiation between risk factors for disease occurrence, those influencing disease progression in a treated or an untreated situation, or those that seem to influence multiple stages is not feasible at the present time. For the purpose of this review, we present supporting evidence for each of the above factors and have summarized studies relevant to risk factors in two tables: one with cross-sectional and one with longitudinal studies.

Non-modifiable background factors

Age

The relationship between age and periodontitis is not straightforward. Early evidence demonstrates that both the prevalence and severity of periodontitis increase with increasing age, suggesting that age may be a marker for periodontal tissue support loss (Van der Velden 1984, 1991, Johnson 1989, Johnson et al. 1989, Burt 1994). However, the belief that periodontitis is a disease of the elderly has been challenged over the years. Instead of indicating an increased susceptibility to periodontitis in older people, this ''age effect'' can conceivably represent the cumulative effect of prolonged exposure to true risk factors (Papapanou et al. 1991). Moreover, it is established that periodontitis may have its onset in youth and early adulthood, rather than in older years (Burt 1992, 1994). Therefore, a subject's susceptibility level to periodontal disease appears to be more important than age, and subjects with high susceptibility manifest the disease at an earlier age (Van der Velden 1991, Albandar et al. 1999). Notably, the effect of age appears to be different for PD and CAL. Specifically, while there is a pronounced effect of increasing CAL with age, the effect on PD appears to be minimal (Albandar 2002a, b). Interestingly, the effect of age on CAL has been found to be reduced after adjusting for covariates such as oral hygiene levels or access to dental care services (Albandar 2002a). However, studies have often failed to adjust for important covariates such as systemic diseases (e.g., diabetes) and health-risk behaviours (e.g., smoking) in the older population. Therefore, the literature on the effect of age on periodontitis needs to be interpreted with caution.

Gender

Although there is no established, inherent difference between men and women in their susceptibility to periodontitis, men have been shown to exhibit worse periodontal health than women (Burt & Eklund 1999, 2000b, Albandar 2002a). This difference has been documented in different populations (National Institute Dental Research 1985 national survey, Burt & Eklund 1999, Albandar 2002a, b) and has been traditionally thought to be a reflection of better oral hygiene practices (Hugoson et al. 1998, Christensen et al. 2003) and/or more utilization of oral health care services among women (Yu et al. 2001, Dunlop et al. 2002, Roberts-Thomson & Stewart 2003). On the other hand, periodontitis is a bacterial infection determined to a large extent by the host immuno-inflammatory response to the bacterial challenge. Although gender-specific differences in these responses have not been unequivocally demonstrated, it is biologically plausible that such differences do, in fact, exist.

Race/ethnicity

Although differences in the prevalence of periodontitis between countries and across continents have been demonstrated (Baelum et al. 1996, Albandar 2002a), no consistent differences across racial/ethnic groups have been documented when age and oral hygiene are accounted for (Burt & Eklund 1999). Interestingly, most national surveys and local studies in the United States consistently show a racial/ethnic differential pattern in the prevalence of periodontitis: African Americans exhibit the highest prevalence of periodontitis while Mexican Americans exhibit a prevalence similar to non-Hispanic whites. Importantly, this finding has been consistent regardless of the case definition used (Albandar et al. 1999, Arbes et al. 2001, Borrell et al. 2002b, Hyman & Reid 2003). However, race/ethnicity is usually a social construct that determines an array of opportunities in the society such as access, status, and resources (Williams 1997, 1999). As a result, race/ethnicity and SES are strongly intertwined, suggesting that the pervasive racial/ethnic effect is the result of residual confounding by SES because of the unequal meaning of SES indicators across racial/ethnic groups (Williams 1996, Kaufman et al. 1997, Krieger et al. 1997, Lynch & Kaplan 2000). Corroborating this point, a recent study found that African Americans demonstrated a lower benefit from education and income on periodontal health status than their Mexican American and white peers (Borrell et al. 2004). These findings confirm the incommensurability of socioeconomic indicators across racial/ethnic groups and perhaps reflect the historical implications of unequal opportunities for certain ethnic groups in the society.

Gene polymorphisms

Evidence from classical twin studies (Michalowicz et al. 1991) suggests that genetic determinants are significant modifiers of the periodontitis phenotype (Michalowicz 1994, Hart & Kornman 1997, Schenkein 2002), but the role of single-nucleotide polymorphisms remains unclear. After Kornman's seminal work (Kornman et al. 1997) reporting an association of a composite genotype based on specific polymorphisms in the interleukin-1 (IL-1) gene cluster with severe periodontitis in non-smokers, there has been an exponential increase in publications that examined a plethora of gene polymorphisms as severity markers of periodontitis. These include additional investigations of the particular IL-1 gene polymorphism in both cross-sectional/case–control settings (Gore et al. 1998, Diehl et al. 1999, Armitage et al. 2000, Mark et al. 2000, McDevitt et al. 2000, Parkhill et al. 2000, Socrans-

Table 2. Longitudinal studies

Study	Aim/methods	Outcome(s)	Exposure(s)	Results
Beck et al. (1995)	To present the incidence of CAL in subjects who show progressive CAL in sites previously without disease and subjects who experience further progression at sites with pre-existing disease; and to compare and contrast the characteristics of people with the two types of progressive CAL. Exams at 18 and 36 months US $N = 338$ dentate adult aged 65+ blacks (169) and whites (169)	Incidence rates defined as CAL $\geqslant$ 3 mm. Extent and severity	Initial periodontal status: no new CAL; CAL in $\geqslant$ 1 site previously diseased (baseline CAL $<$ 3 mm); CAL $\geqslant$ 1 site previously diseased (baseline CAL $\geqslant$ 3 mm); and those who experienced both new disease and progression of existing disease. Sociodemographic, psychosocial, medical, environmental, behavioural and oral information	The 3-year incidence was 41.3% for those with no progression and no new lesions; 27.5% for those with new lesions only; 11.1% for those with progressing lesions only; and 20.1% for those with both. Income $<$ \$15,000, soft-tissue reaction caused by medication, use of smokeless tobacco, and history of pain were significantly associated with an increased incidence of new lesions. Income $<$ \$15,000, soft-tissue reaction caused by medication, smoking cigarettes, BANA positive test, *Porphyromonas gingivalis*, and financial problems were associated with disease progression
Kaldahl et al. (1996)	To evaluate the effects of the level of cigarette consumption and smoking history on the response to active periodontal treatment and up to 7 years of supportive periodontal treatment. Exams at baseline (Exam 1), 4 weeks after mechanical plaque control instructions (Exam 2), 10 weeks following periodontal surgery (Exam 3), and yearly during 7 years of supportive periodontal treatment. US $N = 74$, with moderate-to-advanced periodontitis	PD, gingival recession, CAL and horizontal probing attachment level; percentage of sites with plaque and BOP	Smoking status: heavy smokers ($\geqslant$ 20 cigarettes/day, $n = 31$); light smokers $\leqslant$ 19 cigarettes/day, $n = 15$); past smokers (had a history of smoking but quit before Exam 1, $n = 10$), and never smokers ($n = 18$)	After 7 years of follow-up, past and never smokers consistently exhibited a significantly greater reduction in PD than heavy and light smokers. Past and never smokers exhibited gains in mean CAL compared with light and heavy smokers. There were no differences in average gingival recession of the mean change in horizontal attachment at furcation sites following active therapy among the four groups. All groups experienced a similar decrease in the prevalence of bleeding sites following active therapy
Beck et al. (1997a)	To examine time-to-event analysis of attachment loss over a 5-year period by a variety of characteristics, and to describe a multivariate logistic regression model with potential risk factors. Exams at 18, 36, and 60 months US $N = 540$ dentate adult aged 65+ (18,947 sites)	Incidence rates defined as CAL $\geqslant$ 3 mm	*Actinobacillus actinomycetemcomitans*, *Prevotella intermedia* and *P. gingivalis*. Age, gender, missing teeth, education, smoking, dental visit	In a multivariate model adjusting for the time intervals, smoking (OR = 1.6; 95% CI: 1.2–2.0), being positive for *P. gingivalis* at baseline (OR = 1.7; 95% CI: 1.3–2.2), having 5 or more missing teeth (OR = 1.9; 95% CI: 1.4–2.7), and not being a high-school graduate (OR = 1.8; 95% CI: 1.4–2.4) were significantly associated with an increased risk for attachment loss. In addition, having a dental visit more than 5 years ago (OR = 1.2; 95% CI: 1.0–1.3) significantly increased the risk
Beck et al. (1997b)	To examine (1) whether attachment loss during one time period is associated with a higher risk for attachment loss at a subsequent period in the same subject; (2) whether sites in survivor teeth with deeper periodontal pockets at baseline are more likely to experience future attachment loss; and (3) whether an effect of regular use of	CAL $\geqslant$ 3 mm over each 18-month period	PD and dental care	Whites tended to be less likely to experience CAL, with 63.5% experiencing no loss over the 5 years compared with 44.1% of blacks experiencing no loss. Sites with CAL in whites had lower RR of CAL than sites for blacks during all 3 periods. Baseline pocket depth and irregular dental visits were positively associated with the proportion of sites that

	dentists' services on attachment loss are demonstrable in a community-dwelling population. Exams at baseline, 18 months, 36 months, and 5 years US $N = 220$ dentate adult aged 65+ blacks (106) and whites (114)			demonstrated breakdown over the next 5 years. Sites with PD > 3 mm at baseline consistently associated with higher percentage of sites with CAL, regardless of race
Firatli (1997)	To examine the clinical status of the periodontal tissues in a group of diabetic subjects over 5 years; and to demonstrate the association between DM and periodontal disease. US $N = 64$ adolescents (44 with type 1 diabetes and 20 without); whites	Plaque and gingival indices, BOP, PD and CAL	Serum fructosamine, glycosylated haemoglobin and glucose levels	Mean CAL significantly increased between baseline (2.39) and the 5-year follow-up (3.51) in the diabetic group. A significant positive correlation was observed between the duration of diabetes and CAL at both baseline and 5-year examination.
Tervonen & Karjalainen (1997)	To assess variations in periodontal status of type 1 diabetic adolescents; and to study the healing and recurrence of periodontal disease after the hygienic phase of periodontal therapy. Exams at 4 weeks, 6 and 12 months. Finland $N = 46$ (36 diabetics and 10 controls) aged 24–36 years	Periodontal status: dental plaque, calculus, PD, BOP and CAL	Diabetic status: D1 ($n = 13$) no diabetic complications and good long-term metabolic control; D2 ($n = 15$) moderate metabolic control with/without retinopathy; D3 ($n = 8$) severe diabetes with poor metabolic control and/or multiple complications	No statistically significant differences in the periodontal health status were observed between the diabetic group as a whole and the non-diabetic controls at any examination. The level of periodontal health of the diabetic patients with good control and no complications (D1) and those with moderate control with/without retinopathy (D2) was similar to non-diabetic controls. Diabetic subjects with poor metabolic control and/or multiple complications (D3) exhibited higher extent of CAL ⩾ 2 mm at baseline and higher recurrence of PD ⩾ 4 mm during follow-up
Baelum et al. (1997)	To describe predictors of new and progressing destructive periodontal disease over a 10-year period in a rural subject sample. China $N = 398$ Aged 20–60+ years	''New disease'' was defined as loss of attachment of 2+ mm, in sites with no CAL at baseline; ''progressing disease'' was defined as additional attachment loss of 2+ mm at sites with pre-existing attachment loss	Other covariates: age; sex; number of mobile teeth; percentage of sites with plaque; percentage of sites with calculus; percentage of sites with BOP; percentage of sites with baseline of CAL 1+, 4+, and 7+ mm; and percentage of sites with PD of 4+ and 7+ mm	Adjusted analyses showed that male gender, lower # of sites present, increasing percentage of existing sites with CAL 4+ mm and increasing number of mobile teeth were predictors of new disease, while younger age, increasing percentage of existing sites with CAL 4+ mm, and PD with 4+ mm were predictors of PDS
Papapanou et al. (1997)	In a sample of rural subjects with limited access to dental care, to describe the prevalence of selected bacterial species; correlate the microbiological and clinical profiles of the subjects; and assess the association between the microbiological variables and the retrospective longitudinal changes of periodontal status occurring over a 10-year period. $N = 148$, 30–39 and 50–59 years old. China	Tooth site-based analysis: ''deep'' sites, if PD ⩾ 5 mm, otherwise ''shallow''; ''progressing'' if 10-year longitudinal CAL loss ⩾ 3 mm, otherwise ''stable''. Subject-based analysis: ''positive'' subject if having ⩾ 3 sites with PD ⩾ 5 mm, otherwise ''negative''; ''downhill'' if having ⩾ 10 sites with 10-year longitudinal CAL loss of ⩾ 3 mm, otherwise ''stable''	A maximum of 14 subgingival plaque samples obtained from each subject (1864 in total); analysed with respect to 18 bacterial species	Ubiquitous prevalence for the majority of the investigated species on the subject level. Bacterial profiles identified ''deep'' sites with 74% sensitivity and 64% specificity. Corresponding figures were 66% and 58% for ''progressing'' sites; 79% and 66% for ''positive'' subjects; and 75% and 85% for ''downhill'' subjects. Bacterial colonization at high levels by *P. gingivalis*, *P. intermedia*, *P. nigrescens*, *T. forsythensis*, *F. nucleatum*, *T. denticola*,

Table 2. (Contd.)

Study	Aim/methods	Outcome(s)	Exposure(s)	Results
				M. micros, and *C. rectus* conferred statistically significant ORs for both ''positive'' and ''downhill'' subjects
Grossi et al. (1997b)	To determine the effect of smoking on the clinical and microbiological response to mechanical periodontal therapy; and to determine the effect of smoking cessation on periodontal therapy. Baseline and 3-month exams US $N = 143$ aged 35–65 years with established periodontitis ($\geqslant 2$ inter-proximal sites with CAL $\geqslant 6$ mm and one inter-proximal site with PD $\geqslant 5$ mm)	PD, CAL, PI, bleeding index	Supragingival scaling and oral hygiene instruction, followed by four to six sessions of subgingival instrumentation. After the first four sessions of subgingival scaling, subjects received one or two additional sessions as needed. Smoking status: current ($n = 60$), former ($n = 55$) and non-smokers ($n = 28$). Overall lifetime exposure to tobacco was quantified in pack-years (# of cigarettes/day $\times$ # of years smoking). Period free or quit years (# of years since smoking was stopped) was also calculated. *T. forsythensis* and *P. gingivalis*	There were no differences in mean CAL and PD at baseline by smoking status. After 3 months, there was a significant reduction in whole-mouth mean PD, with current smokers showing less reduction ($p < 0.04$) than former- and non-smokers (0.33+0.04, 0.49+0.06 and 0.49+0.08, respectively). Current smokers exhibited less CAL gain than former and non-smokers (0.32+0.04, 0.43+0.06 and 0.39+0.08, respectively). At baseline, only current smokers showed higher proportion of *T. forsythensis* ($p < 0.04$) and *P. gingivalis* (NS) compared with former and non-smokers. After treatment, fewer smokers harboured no *P. gingivalis* ($p < 0.008$) or *T. forsythensis* (NS) compared with former and non-smokers. Among subjects positive for these pathogens, current smokers exhibited the highest proportions.
Taylor et al. (1998a)	To test the hypothesis that the risk for progressive severe alveolar bone loss is greater in subjects with PC type 2 DM, compared with those without type 2 DM or with BC type 2 DM. Two-year study US $N = 359$ adults aged 15–57 years (338 diabetes free, 14 with PC and seven with BC type 2 DM) Native Americans	Alveolar bone loss: the worst bone score in the dentition was categorized as 0%; 1–24%; 25–49%; 50–74%; and $\geqslant 75\%$ of the root length. Progression of bone loss: difference between baseline worst score and worst score at follow-up.	Glycaemic control: BC (HbA_1 <9%) and PC ($HbA_1 \geqslant 9\%$). Age, calculus, gingival and plaque indices, time to follow-up, alcohol consumption, smoking, obesity (BMI > 27), coronary heart disease, and gender	In multiple logistic regression, PC diabetic subjects were 11 times more likely (95% CI: 2.5–53.3) to have more bone loss and more pronounced bone loss progression than non-diabetic subjects, but there were no such differences between BC and no-diabetic controls. When compared with BC, PC subjects were five times more likely to have more severe alveolar bone loss and more pronounced bone loss progression but this association did not reach statistical significance. Age, time to follow-up, worst bone loss at baseline and calculus index were significant predictors of bone loss progression.
Taylor et al. (1998b)	To test the hypothesis that persons with NIDDM have greater risk of more severe alveolar bone loss progression over a 2-year period than those without NIDDM. 2-year study US $N = 359$ adults aged 15–57 years (24 subjects with NIDDM) Native Americans	Same as Taylor et al. (1998a)	Diabetes defined by a plasma glucose concentration $\geqslant 200$ mg/dl 2 h after a 75-g oral glucose load. Covariates: age, calculus, gingival and plaque indices, time to follow-up, number of teeth, alcohol consumption, smoking, obesity (BMI > 27), systolic blood pressure, coronary heart disease, and gender	Compared with non-diabetic subjects, NIDDM patients showed an increasing trend for more bone loss at follow-up. When stratifying by baseline worst bone score, NIDDM patients with 0% score had a greater bone loss progression than their counterparts with a score of 1–24%. NIDDM was associated with a 4.23 times increased risk (95% CI: 1.8–9.9) of change to a worse bone score when compared with non-diabetics. This association was modified by age, with younger adults

				exhibiting higher risk for alveolar bone loss progression. Age, time to follow-up, worst bone score at baseline and calculus were independent predictors of bone loss progression
Machtei et al. (1999)	To explore longitudinally a variety of clinical, systemic, and microbiological markers as possible risk factors in subjects with mild periodontal disease. 2–4-year follow-up. US $N = 415$ aged 25–75 years whites (95.6%)	PI, gingival index, PD, RAL, CAL, ACH. Progression of disease was measured as annual change in PD, CAL, percentage of losing and gaining sites.	*A. actinomycetemcomitans*, *T. forsythensis*, *C. rectus*, *P. intermedia*, *Capnocytophaga* species, *P. gingivalis*, *E. saburreum*, *F. nucleatum*. Covariates: age, gender, smoking (current smokers 15.4%), education, income	Approximately 10% of all sites presented for the second visit with attachment loss exceeding 2 mm (4.4% annually), while only 2.2% of all sites exhibited attachment gain (0.9% annually). The percentage of sites losing ACH was 9.4%. Stepwise regression showed that baseline PD, income, presence of *capnocytophaga* species, smoking, and thyroid disorder were significant predictors of annual change in PD. Past disease history, SES, smoking, presence of *T. forsythensis and Capnocytophaga* species, dental visits, and several systemic conditions were significant predictors of annual change on CAL and ACH and tooth loss.
Norderyd et al. (1999)	To identify risk factors for severe periodontal disease progression in adults. Approximately 16 years of follow-up Sweden $N = 361$ aged 20–60 years	Proximal bone level was measured as percentage of the tooth length. The annual periodontal bone loss was calculated based on a mean tooth length of 22 mm for the entire dentition (third molars were excluded). Periodontal disease progression was defined as $>20\%$ bone loss at a proximal site	Covariates: age, supragingival plaque, gingival inflammation, and probing pockets 4+ mm	Age, smoking, supragingival plaque, gingival inflammation and PD 4+ mm were associated with an increase of proximal bone loss of $>20\%$ in 6+ sites. After adjustments, age, female gender, high income, smoking, and PD 4+ mm were associated with increased proximal bone loss
Bergström et al. (2000a)	To prospectively investigate the influence of smoking over 10 years on the periodontal conditions of a dentally aware population of musicians. Sweden $N = 84$; 16 current smokers, 28 former- and 40 non-smokers	Periodontal disease was defined by the percentage of sites with 4+ mm of PD on each occasion (''diseased sites''). Proportion of sites with GB. Bone height: mean percentage of the root length mesially and distally to all teeth excluding third molars	Smoking: number of cigarettes/day, numbers of years, lifetime exposure (cigarette/day $\times$ years). Other covariates: age, PI	The prevalence of diseased sites was 18.7% for current, 11.1% for former-, and 8.7% for non-smokers at baseline. At 10 years, these figures were 41.6%, 7.8%, and 6.6%. For current smokers, the deterioration increased significantly with increasing cigarette consumption, smoking duration, and lifetime exposure. The mean level of bone height at baseline was 80.3% for current-, 80.7% for former- and 85.1% for non-smokers. At 10 years, there was a significant decrease in mean values for current (76.5%) and former smokers (79.6%) when compared with non-smokers (84.1%). There was no significant difference in GB between baseline and follow-up between smoking groups. There was no significant difference between number of teeth present at baseline and follow-up across smoking groups. After adjusting for age, GB, PI, and frequency of diseased sites at baseline, the 10-year

Table 2. (Contd.)

Study	Aim/methods	Outcome(s)	Exposure(s)	Results
				change in the frequency of diseased sites was predicted by current smoking ($p = 0.039$)
Timmerman et al. (2000)	To assess the impact of clinical and microbiological baseline characteristics on periodontal disease progression over 7 years. Indonesia $N = 255$ aged 15–25 years tea labourers with low education	PDS $\geqslant$ 1 site with CAL $\geqslant$ 2 mm	PI, BOP, PD, and CAL score on the buccal aspect of all teeth. *A. actinomycetemcomitans, P. gingivalis, P. intermedia,* spirochetes, and motile microorganisms. Age and gender	Out of 255 subjects available at baseline, 160 were re-examined at 7 years. At follow-up, all clinical measures with the exception of PD showed a statistical increase that was greater in subjects with PDS at baseline. Presence of *A. actinomycetemcomitans* (OR = 4.2; 95% CI: 1.4–12.7), *P. gingivalis* (OR = 2.3; 95% CI: 1.0–5.2) and motile microorganisms (OR = 2.2; 95% CI: 1.0–5.0) were associated with PDS at follow-up. In a multivariable logistic model, age (OR = 1.15, $p = 0.04$), subgingival calculus (OR = 1.20, $p = 0.02$), and subgingival presence of *A. actinomycetemcomitans* (OR = 4.61, $p = 0.01$) were associated with PDS at follow-up
Chen et al. (2001)	To examine whether salivary and/or GCF cotinine levels were associated with the severity of periodontal disease in smokers and non-smokers. 10-year study China $N = 177$ male farmers, aged 30–69 years	Cotinine in saliva and in GCF. Smoking status: smokers ($\geqslant$ 2 cigarettes/day, 20 days/month) and non-smokers	PD, CAL, plaque, calculus, and GB. Other covariates: age, packs smoked per year, years smoking	Cigarette smoking was associated with a greater increase in PD and attachment loss, as well as greater tooth loss at an earlier age. All smokers had detectable salivary and GCF cotinine. However, neither salivary cotinine nor GCF cotinine was significantly correlated with PD, attachment loss, and tooth loss ($p > 0.05$)
Stewart et al. (2001)	To compare changes in glycaemic control in a group of patients with type 2 DM following periodontal treatment, to a control group with type 2 DM who did not receive periodontal treatment. 18 months US $N = 72$, equally divided between treatment and control groups	Periodontal treatment group: root planing, subgingival curettage and extractions. Control group: no dental treatment	Glucose control: % HbA1c. Covariates: age, race	Patients receiving periodontal treatment showed a decrease of 17.1% ($p = 0.0001$) in HbA1c levels, while the control group showed a decrease of 6.7% ($p = 0.02$). Changes in HbA1c were statistically significant for those receiving oral hyperglycaemic agents (18%, $p = 0.0005$) and insulin (18%, $p = 0.003$) in the treatment group only.
Cullinan et al. (2001)	To investigate the relationship between IL-1 genotype and periodontitis. 5-year study Australia $N = 295$	PD and CAL at 6, 12, 24, 36, 48, and 60 months. Periodontitis progression: CAL $\geqslant$ 2 mm at any period of exam during the 5 years	SNPs at IL-1A (+4845T) and IL-1B (+3954T). *A. actinomycetemcomitans, P. intermedia*, and *P. gingivalis*. Age, gender, smoking	The prevalence of the composite genotype consisting of the less common allelic variants was 39%. A relationship was found between the IL-1 positive genotype and increased mean probing pocket depth in non-smokers > 50 years old. IL-1 genotype-positive smokers and genotype-positive subjects with *P. gingivalis* had a higher number of sites with PD $\geqslant$ 3.5 mm. There was a trend for IL-1 genotype-positive subjects to experience higher periodontitis progression than IL-1 genotype-negative subjects.

Ogawa et al. (2002)	To identify risk factors for periodontal disease progression among elderly people over a 2-year period. Japan $N = 554$ (281 males and 273 females) at baseline, $N = 394$ (208 males and 186 females) at follow-up	Periodontal disease progression defined as $\geqslant 1$ site with $\geqslant 3$ mm longitudinal CAL between the two examinations	Covariates: gender, smoking, alcohol, use of dental care, dental visits per year, dental self-care behaviours, CAL$\geqslant$6 mm, and number of teeth present. Blood pressure, serum markers of liver disease (GOT, GPT and γ-GTP), kidney disease (creatinine), immunoglobulins (IgG, IgA and IgM), lipid profiles (total cholesterol and triglycerides), and nutritional factors (total-protein, calcium, blood-sugar, and albumin)	75.1% of the study population exhibited an additional CAL 3+ mm at one or more sites after 2 years. Males, smokers, and subjects with CAL 6+ mm at baseline were more likely to lose an additional 3+ mm of CAL. In the multivariable analyses, smoking, gender, CAL $\geqslant$6 mm, and $\geqslant$20 remaining teeth were associated with disease progression
Rodrigues et al. (2003)	To compare changes in glycaemic control in a group of patients with type 2 DM following full-mouth scaling and root planing alone or in combination with amoxicillin/clavulanic acid. 3-month follow-up. Brazil $N = 30$ with chronic periodontitis	Chronic periodontitis: at least 1 site with PD$\geqslant$5 mm and 2 teeth with CAL$\geqslant$6 mm	Subjects randomly assigned to full-mouth scaling and root planing alone ($N = 15$; G2) and in combination with amoxicillin/clavulanic acid ($N = 15$; G1). HbA1c and fasting glucose levels assessed at baseline and 3 months	HbA1c values were reduced for both groups between baseline and 3 months. However, only the changes in G2 were statistically significant ($8.8 \pm 1.8\%$ *versus* $7.6 \pm 1.4\%$, $p = <0.05$). Baseline mean fasting glucose levels for both groups were statistically different ($p<0.05$); G1: 221 ± 60 mg/dl and G2: 175 ± 68 mg/dl. There was no difference between groups in the mean fasting glucose levels at 3 months.

CAL, clinical attachment level; RR, relative risk; OR, odds ratio; CI, confidence interval; PD, probing depth; PC, poorly controlled; DM, diabetes mellitus; BC, better controlled; NIDDM, non-insulin-dependent diabetes mellitus; BMI, body mass index; RAL, relative attachment level; ACH, alveolar crestal height; SES, socioeconomic status; PDS, progressive disease; PI, plaque index; BOP, bleeding on probing; GCF, gingival crevicular fluid; GB, gingival bleeding; IL, interleukin; SNP, single-nucleotide polymorphism; HbA1c, glycated haemoglobin.

ky et al. 2000, Walker et al. 2000, Hodge et al. 2001, Laine et al. 2001, Papapanou et al. 2001, Caffesse et al. 2002, Meisel et al. 2002, 2003, 2004; Anusaksathien et al. 2003, Gonzales et al. 2003, Guzman et al. 2003, Sakellari et al. 2003, Li et al. 2004, Quappe et al. 2004, Scapoli et al. 2005) and longitudinal studies (Ehmke et al. 1999, De Sanctis & Zucchelli 2000, Lang et al. 2000, Cullinan et al. 2001, Christgau et al. 2003, Jepsen et al. 2003), as well as studies of other gene polymorphisms such as the IL-1 receptor antagonist (Tai et al. 2002); IL-6 (Anusaksathien et al. 2003, Trevilatto et al. 2003); IL-10 (Kinane et al. 1999, Yamazaki et al. 2001, Gonzales et al. 2002, Berglundh et al. 2003, Scarel-Caminaga et al. 2004); IL-4 (Michel et al. 2001, Scarel-Caminaga et al. 2003, Gonzales et al. 2004, Pontes et al. 2004); IL-2 (Scarel-Caminaga et al. 2002); tumour necrosis factor (Galbraith et al. 1998, Endo et al. 2001, Shapira et al. 2001, Craandijk et al. 2002, Fassmann et al. 2003, Soga et al. 2003, Perez et al. 2004, Shimada et al. 2004); transforming growth factor-β 1 (TGF-β 1) (Holla et al. 2002b); Fc receptor of immunoglobulin G (IgG) (Kobayashi et al. 1997, 2000a, b, 2001, Sugita et al. 1999, 2001, Meisel et al. 2001, Chung et al. 2003, Loos et al. 2003, Yasuda et al. 2003, Yamamoto et al. 2004); CD14 receptor (Holla et al. 2002a); vitamin D receptor (Hennig et al. 1999, Tachi et al. 2003, de Brito et al. 2004); N-acetyltransferase 2 (Meisel et al. 2000, Kocher et al. 2002); and matrix metalloproteinase 1 and 3 (Holla et al. 2004, Itagaki et al. 2004).

Typically, the majority of the cross-sectional studies above report positive associations between the investigated polymorphisms and the extent or the severity of periodontitis. The results, however, are not unequivocal, as the strength of the reported associations is not uniformly consistent across populations, the frequency of occurrence of these polymorphisms appears to vary extensively between ethnic groups, the subject samples involved are generally of limited size, the definitions of the outcome variable (periodontitis) vary considerably, and adjustments for other important covariates and risk factors have frequently not been performed. Importantly, there appear to be differences in the impact of these polymorphims on early-onset *versus* adult forms of periodontitis. For example, in the case of IL-1 polymorphisms, while it is

the rare allele (allele 2) that has been linked with severe disease in adults, it is allele 1 that has been found to be more prevalent in subjects with early-onset periodontitis (Diehl et al. 1999, Parkhill et al. 2000).

The relatively few longitudinal studies that have studied specific gene polymorphisms as exposures are similarly conflicting. Ehmke et al. (1999) reported no bearing of the IL-1 gene polymorphism on the prognosis of periodontal disease progression following non-surgical periodontal therapy. Jepsen et al. (2003) failed to provide evidence that the IL-1 risk genotype was associated with higher gingival crevicular fluid (GCF) volume and percentage BoP during the development of experimental gingivitis. In contrast, Lang et al. (2000) concluded that IL-1 genotype-positive subjects have a genetically determined hyper-inflammatory response that is expressed clinically in the periodontal tissues as increased BoP prevalence and incidence during maintenance. Three treatment studies examined the impact of this particular polymorphism in regenerative therapy: De Sanctis & Zucchelli (2000) reported that the IL-1-positive genotype was associated with inferior long-term outcome of regenerative therapy of intrabony defects. In contrast, Christgau et al. (2003) and Weiss et al. (2004) failed to document such an association in similar studies of the regenerative potential of such defects. Finally, in a 5-year prospective study of 295 subjects, Cullinan et al. (2001) reported an interaction between the positive genotype, age, smoking, and colonization by *Porphyromonas gingivalis* and concluded that the positive genotype is a contributory but non-essential factor for the progression of periodontal disease.

In conclusion, there is insufficient epidemiologic evidence that convincingly establishes any of the above polymorphisms as true risk factors for periodontitis.

Environmental, acquired, and behavioural factors

SES

Previous studies have documented differences in periodontal health by socioeconomic indicators, i.e., income and education (Nikias et al. 1977, Oliver et al. 1991, 1998, Locker & Leake 1993, Cherry-Peppers et al. 1995, Elter et al. 1999, Borrell et al. 2002a, b), but these indicators have rarely been investigated as independent variables of main interest. These studies can be summarized as those reporting (i) higher rates of disease for subjects with low SES in cross-tabulations between outcomes and socioeconomic indicators (Beck et al. 1990, 1995, 1997a, Locker & Leake 1993, Borrell et al. 2002a, b), or (ii) that racial/ethnic differences persisted after adjustment for socioeconomic indicators in multivariate analyses (Ismail et al. 1983, Brown et al. 1994, Tonetti 1998, Tomar & Asma 2000, Haffajee & Socransky 2001). Regardless, socioeconomic indicators are robust markers of periodontitis. Their role in periodontal disease can be attributed to differential access to resources and opportunities that may influence preventive behaviours. Evidence also suggests that education has a greater influence than income in favourably affecting the level of periodontitis in the population (Borrell et al. 2004).

Specific microbiota

In a classic paper, Haffajee & Socransky (1994) adapted Koch's postulates to be used in the identification of periodontal pathogens and proposed the following criteria: (i) association, i.e., elevated odds ratios in disease; (ii) elimination, i.e., conversion of disease to health when bacteria are suppressed; (iii) development of a host response; (iv) presence of virulence factors; (v) evidence from animal studies corroborating the observations in humans; and (vi) support from risk assessment studies. Based on the above criteria, the Consensus Report of the 1996 World Workshop in Periodontics identified three species (*Actinobacillus actinomycetemcomitans, P. gingivalis*, and *Bacteroides forsythus*, recently renamed *Tanerella forsythensis*; Sakamoto et al. 2002, Maiden et al. 2003) as causative factors for periodontitis. Given that approximately 50% of the bacteria of the oral cavity are currently recognized (Paster et al. 2001), it is clear that these three species cannot be considered to be the only causative pathogens, but are rather the ones for which sufficient data have accumulated.

Over the last decade, interesting data have emerged on the prevalence of these causative bacteria in different populations, in states of both periodontal health and disease. Studies performed in children (Tanner et al. 2002, Yang et al. 2002) that analysed plaque from the gingival crevice, tooth surface, and the dorsum of the tongue revealed that sizeable proportions of subjects harboured *P. gingivalis*, *T. forsythensis*, and *A. actinomycetemcomitans* despite absence of overt gingival inflammation. A comparably high carrier state was documented in studies that sampled infants, children, adolescents, and adults with good clinical periodontal status (Könönen 1993, McClellan et al. 1996, Kamma et al. 2000, Lamell et al. 2000). Thus, contrary to the conclusions of earlier, culture-based studies that these bacteria occur infrequently in periodontally healthy oral cavities and behave as exogenous pathogens, the above studies that have used molecular techniques for bacterial identification demonstrate the contrary. However, both the prevalence of and the level of colonization by these pathogens have been shown to vary significantly between populations of different racial or geographic origin (Ali et al. 1994, Sanz et al. 2000, Haffajee et al. 2004, Lopez et al. 2004).

Several epidemiological studies have examined the prevalence of the established periodontal pathogens and its relation to clinical periodontal status in population samples from both developed and developing countries. Griffen et al. (1998) examined a convenience sample recruited from a university clinic, and reported that 79% of the diseased and 25% of the healthy subjects were positive for *P. gingivalis*. Interestingly, the prevalence of *P. gingivalis* in the periodontally healthy group varied substantially with race/ethnicity, as it occurred in 22% of Whites, 53% of African Americans, and 60% of Asian Americans. In a case–control study of periodontitis patients and age- and gender-matched controls with no or only minimal attachment loss in Sweden, Papapanou et al. (2000) reported a high prevalence of *P. gingivalis*, *A. actinomycetemcomitans*, *T. forsythensis*, and *Treponema denticola* in periodontitis patients (95%, 83%, 97%, and 93%, respectively), but also similarly high prevalence rates among control subjects (82%, 90%, 82%, and 94%). However, in a quantitative analysis of bacterial load, substantial differences in colonization at high levels (i.e., at an average count $\geqslant 10^5$ bacterial cells/plaque sample) were observed between patients and controls for three of the four bacteria:

19% *versus* 3% for *P. gingivalis*, 54% *versus* 12% for *T. forsythensis*, and 46% *versus* 19% for *T. denticola*. In contrast, corresponding percentages were similar for *A. actinomycetemcomitans* (1% in both cases and controls). Substantially different prevalence data were reported in a study of blue- and white-collar University employees in Australia (Hamlet et al. 2001). These authors detected *A. actinomycetemcomitans* in 23% and *P. gingivalis* in 15% of the subjects.

A number of studies investigated the epidemiology of periodontal pathogens in Asian populations. Timmerman et al. (1998) examined a sample of adolescents in rural Indonesia, and detected *P. gingivalis* in 87% and *A. actinomycetemcomitans* in 57% of the subjects. Mombelli et al. (1998) examined young factory workers in China and detected *A. actinomycetemcomitans* in 62% and *P. gingivalis* in 55% of the subjects. In contrast, an almost ubiquitous presence of *P. gingivalis* and *T. forsythensis* was reported in rural subject samples in China (Papapanou et al. 1997) and Thailand (Papapanou et al. 2002), while *A. actinomycetemcomitans* was detected in 83% and 93% of the subjects in the Chinese and Thai samples, respectively. Despite this high prevalence, a quantitative analysis of bacterial load correlated well with periodontal status in both studies. For example, a discriminant analysis performed on the data from the Thai study (Papapanou et al. 2002) identified threshold levels of average bacterial load, which, when exceeded, conferred increased odds for presence of $\geqslant 3$ sites with pocket depth $\geqslant 5$ mm. For three species (*P. gingivalis*, *T. forsythensis*, and *T. denticola*), colonization above these calculated thresholds resulted in statistically significant, elevated odds for periodontitis. In addition, an analysis of the association between colonization at high levels by the ''red complex'' bacteria (Socransky et al. 1998) and specific periodontal conditions, defined in this particular study by the presence of $\geqslant 3$ sites with pocket depth $\geqslant 5$ mm and by two different levels of extent of periodontal tissue loss ($\geqslant 10$ and $\geqslant 30$ sites with $\geqslant 5$ mm attachment loss, respectively), revealed statistically significant odds ratios ranging between 3.7 and 4.3 for the ''red complex'' bacteria and all three disease definitions. Similar cross-sectional associations of statistically significant odds ratios for severe periodontitis conferred by specific bacteria have also been observed in several other studies involving subject samples from the western world (Grossi et al. 1994, 1995, Alpagot et al. 1996, Craig et al. 2001).

Importantly, the association between high levels of colonization by specific periodontal pathogens and the progression of periodontal disease has been corroborated by longitudinal data in untreated populations. For example, in the study by Papapanou et al. (1997), a discriminant analysis based on quantitative assessments of subgingival bacterial load correctly classified the substantial majority of the subjects with progression of periodontitis over a preceding 10-year period. Indeed, bacterial profiles correctly classified 75% of the subjects with $\geqslant 10$ sites with longitudinal attachment loss of $\geqslant 3$ mm, and 85% of those who remained stable over the observation period. In a 7-year follow-up study of Indonesian adolescents (Timmerman et al. 2000, 2001), it was shown that subgingival presence of *A. actinomycetemcomitans* was associated with disease progression, defined as the presence of longitudinal attachment loss of $\geqslant 2$ mm. In a follow-up of 2–5-year duration, Machtei et al. (1999) reported that subjects colonized by *T. forsythensis* at baseline exhibited greater alveolar bone loss, a larger proportion of ''loser'' sites, and twice as high longitudinal tooth loss than non-colonized subjects. In a 3-year study, Hamlet et al. (2004) reported odds ratios of 8.16 for attachment loss in adolescents with persistent colonization with *T. forsythensis*.

In conclusion, data generated in the past decade have enhanced our knowledge on a number of specific microbial risk factors for periodontitis, but have also clarified the significance of the concept of bacterial load rather than that of mere positive colonization.

Cigarette smoking

Cigarette smoking has been strongly associated with both the prevalence and the severity of periodontitis, and this association emerges in both cross-sectional and longitudinal studies (Bergström & Preber 1994, Martinez Canut et al. 1995, Albandar et al. 2000, Bergström et al. 2000a, b). Table 1 includes several studies that have investigated the effect of smoking on periodontal status either as the main exposure of interest or as a covariate, and all reported a positive association between smoking and periodontal disease severity regardless of the ''case'' definition of periodontitis used (Grossi et al. 1994, 1995, Martinez Canut et al. 1995, Alpagot et al. 1996, Bridges et al. 1996, Albandar et al. 2000, Boström et al. 2000, McDevitt et al. 2000, Bergström et al. 2000b). Importantly, a dose–response effect has been demonstrated in several studies (Grossi et al. 1994, 1995, Martinez Canut et al. 1995, Bergström et al. 2000b). In longitudinal studies (Table 2), smoking has been found to confer a statistically significant increased risk for periodontitis progression after adjustment for other covariates (Beck et al. 1995, 1997a, Machtei et al. 1999, Norderyd et al. 1999, Chen et al. 2001, Ogawa et al. 2002). An interesting alternative interpretation was put forward by Faddy et al. (2000) who, using 3-year longitudinal data from 504 subjects and applying analytical methods that accommodate serial dependence, suggested that smoking inhibits the normal healing process of the periodontal tissues rather than promoting disease progression.

Importantly, studies examining the effects of smoking on the outcome of periodontal treatment have demonstrated that treatment responses are modified by cigarette consumption, with current smokers exhibiting poorer responses than former or never smokers (Ah et al. 1994, Kaldahl et al. 1996, Renvert et al. 1996, Grossi et al. 1997b, Kinane & Radvar 1997, Boström et al. 1998b, Machtei et al. 1998, Tonetti et al. 1998, Scabbia et al. 2001, Trombelli et al. 2003, Van der Velden et al. 2003, Papantonopoulos 2004, Paulander et al. 2004, Rieder et al. 2004, Stavropoulos et al. 2004, Sculean et al. 2005). Notably, these studies have confirmed the negative effect of smoking on the outcome of several periodontal treatment modalities including non-surgical, surgical, and regenerative periodontal therapy.

In conclusion, cigarette smoking appears to fulfill the majority of the required steps of the risk assessment process stipulated by Beck (1994). Admittedly, there is mostly indirect evidence on the benefits of smoking cessation strategies on the periodontal status, mainly inferred based on favourable comparisons between current and former smokers, as well as based on data suggesting that subjects who quit smoking suffer less tooth loss than current smokers (Krall et al. 1997). Importantly, several biologically plausible mechanisms by which smoking exercises its deleterious effects on the periodontal

tissues have been identified, including effects on periodontal microbiota, and the function of several host cells (PMN cells, lymphocytes, fibroblasts). These mechanisms are reviewed in another section of the present workshop.

Diabetes mellitus

Studies performed over the last decade have expanded the available evidence on the role of diabetes mellitus as a major risk factor for periodontitis, especially in subjects with poor metabolic control and a long duration of the disease (Taylor et al. 1996, 1998a, Grossi & Genco 1998, Lalla et al. 2004). Studies suggest a two-way relationship between diabetes and periodontitis, with more pronounced periodontal tissue destruction in people with diabetes but also a poorer metabolic control of diabetes in subjects with periodontitis (Lalla et al. 2000, Soskolne & Klinger 2001, Taylor 2001). Evidence from cross-sectional and longitudinal studies (Tables 1 and 2) suggests that, irrespective of the case definition used for periodontitis, subjects with diabetes have higher prevalence, extent, and severity of periodontal disease (Grossi et al. 1994, Bridges et al. 1996, Firatli 1997, Tervonen & Karjalainen 1997, Taylor et al. 1998a, b, Lalla et al. 2004). These observations are consistent for both Type-1 and Type-2 diabetes. In addition, these studies provide evidence of a dose–response relationship between poor metabolic control and the severity of periodontitis (Tervonen & Karjalainen 1997, Taylor et al. 1998a, Guzman et al. 2003). In line with the above observations, the outcome of periodontal treatment in well-controlled diabetic patients is similar to that of non-diabetic subjects, while poorly controlled diabetics display an inferior outcome (Tervonen & Karjalainen 1997).

New data have also accumulated on the effect of periodontitis on the glycaemic control of the diabetic patient in both type-1 (Aldridge et al. 1995) and type-2 disease (Grossi et al. 1997a, Stewart et al. 2001, Rodrigues et al. 2003). While Aldridge et al. (1995) failed to detect a significant effect of periodontal therapy on the metabolic control of type-1 patients with no other complications irrespective of whether they had gingivitis, incipient periodontitis, or severe periodontitis, a study of patients with type-2 diabetes (Grossi et al. 1997a) reported a 10% improvement in glycated haemoglobin (HbA1c) at 3 months after the completion of non-surgical periodontal therapy combined with adjunctive systemic doxycycline, although this effect was not sustainable at later time points. Interestingly, no such effect on HbA1c was observed in subjects who did not receive adjunctive antibiotic therapy. Stewart et al. (2001) followed 72 patients with type-2 diabetes, half of whom received mechanical periodontal therapy, for 18 months. Patients in both groups showed statistically significant decreases in HbA1c levels (a 17.1% reduction in the treatment group and a 6.7% in the control group). Rodrigues et al. (2003) randomly assigned 30 type-2 patients to two treatment groups, one group receiving non-surgical periodontal therapy with amoxicillin/clavulanic acid and the other receiving only mechanical therapy. At 3 months, HbA1c levels were reduced in both groups, but the reduction was statistically significant only in the group that received scaling and root planing alone.

Thus, it appears that although the role of diabetes mellitus as a risk factor for periodontitis has been clearly established, further studies are needed to clarify the conditions under which periodontal treatment can contribute to improved metabolic control, especially in type-1 diabetes.

Obesity

The biological plausibility of a potential link between obesity and periodontitis has been suggested to involve the hyperinflammatory state and the aberrant lipid metabolism prevalent in obesity, as well as the pathway of insulin resistance (Saito et al. 1998, Nishimura & Murayama 2001), which may collectively result in an enhanced breakdown of the periodontal tissue support. Indeed, a number of recent studies point to a positive association between obesity, defined as body mass index (BMI) $\geqslant 30$, and periodontitis (Journal of the American Dental Association 2000a, Saito et al. 2001, Al-Zahrani et al. 2003, Wood et al. 2003).

Three separate publications have documented such an association in the NHANES III database. In the first publication (Burt & Eklund 2000a), overweight subjects in the upper quartile of insulin resistance index were 1.5 times more likely to have periodontitis compared with their counterparts with a high BMI but a low insulin-resistance index. Al-Zahrani and colleagues (2003) reported a significant association between both BMI and waist-to-hip ratio and periodontitis in younger adults, but no association in middle-aged or older adults (Table 1). Wood et al. (2003), using a subset of the NHANES III sample including Caucasian subjects aged 18 years and above, reported that BMI, waist-to-hip ratio, visceral fat, and fat-free mass were associated with periodontitis after adjusting for age, gender, history of diabetes, current smoking, and SES.

In an independent subject sample including 643 apparently healthy Japanese adults, Saito et al. (2001) reported that waist–hip ratio, BMI, and body fat were significant risk indicators for periodontitis after adjustments for known risk factors. In addition, in a separate analysis of the subsample of subjects with high waist–hip ratio, higher BMI and increased body fat significantly increased the adjusted risk of periodontitis, when compared with subjects with low waist–hip ratios, BMI or body fat.

Given that the above publications are based on only two population samples, and that inferences on temporality or mechanisms are not possible based on cross-sectional studies, additional research on the role of obesity in periodontitis is warranted.

Osteopenia/osteoporosis

A number of cross-sectional studies of limited sample size and largely confined to postmenopausal women have suggested that women with low bone mineral density are more likely to have CAL, gingival recession, and/or pronounced gingival inflammation (von Wowern et al. 1994, Mohammad et al. 1996, 1997, Tezal et al. 2000). However, studies that failed to report such an association have been published as well (Weyant et al. 1999, Lundström et al. 2001).

Based on these studies, it has been hypothesized that the systemic loss of bone density in osteoporosis may, in combination with hormone action, heredity, and other host factors, provide a host system that is increasingly susceptible to the infectious destruction of periodontal tissue (Wactawski-Wende 2001). However, the data from longitudinal studies are similarly conflicting: Contrary to Payne et al. (1999, 2000), who reported an enhanced longitudinal alveolar bone loss in osteoporotic women *versus* women with normal

mineral bone density, Reinhardt et al. (1999) reported no significant impact of serum oestradiol levels on longitudinal attachment loss over a 2-year period. In the most recent study available, Yoshihara et al. (2004) reported, after adjustments, a significant association between bone mineral density and 3-year longitudinal attachment loss in Japanese subjects $\geqslant 70$ years old.

HIV infection

After the early studies published in the late 1980s, which seemed to indicate that both the prevalence and the severity of periodontitis were exceptionally high in patients with AIDS (Winkler & Murray 1987), a more tempered picture has emerged in subsequent publications. While it cannot be ruled out that the initial reports actually included biased population samples, it is also possible that the successful control of immunosupression in HIV-positive subjects by means of high-activity anti-retro-viral therapy and other continuously evolving drugs has influenced the incidence of periodontal disease progression in HIV-seropositive subjects, and has resulted in less severe periodontal manifestations of the HIV infection (Chapple & Hamburger 2000). Thus, although several publications of the last decade continue to report increased prevalence and severity of periodontitis in HIV-positive subjects when compared with controls (Smith et al. 1995, Robinson et al. 1996, Ndiaye et al. 1997, McKaig et al. 1998), other studies are either not supportive of this notion or indicate that the differences in periodontal status between HIV-seropositive and HIV-seronegative subjects are much more limited than earlier believed (Cross & Smith 1995, Lamster et al. 1997, 1998, Scheutz et al. 1997, Vastardis et al. 2003).

In a small follow-up study of 12-month duration, Robinson et al. (2000) found no difference in the progression of periodontitis between HIV-positive and HIV-negative subjects, while Hofer et al. (2002) demonstrated that compliant HIV-positive subjects can be successfully maintained in a manner similar to non-infected controls. Interestingly, recent studies showed that the specific IgG subclass responses to periodontopathic bacteria were similar in HIV-positive and HIV-negative subjects (Yeung et al. 2002), while CD4 count levels were not found to correlate with the severity of periodontitis (Martinez Canut et al. 1996, Vastardis et al. 2003).

Psychosocial factors

The mechanisms by which psychosocial stress may affect periodontal health are complex. It has been suggested that one of the plausible pathways may involve behavioural changes leading to smoking and poor oral hygiene that, in turn, may affect periodontal health (Genco et al. 1998). Without a biological measure of stress per se, a limited number of studies have used proxy measures of stress to study its association with periodontitis. In a study of 1426 subjects in Erie County, NY, USA, Genco et al. (1999) reported that adult subjects who were under financial strain and exhibited poor coping behaviours were at increased risk for severe periodontitis when compared with subjects who demonstrated good coping behaviour patterns under similar financial strain, or with controls under no financial strain. In a study of limited size that included 23 employed adults, Linden et al. (1996) evaluated the association between occupational stress and the progression of periodontitis and reported that longitudinal attachment loss was significantly predicted by increasing age, lower SES, lower job satisfaction and type A personality, characterized by aggressive, impatient, and irritable behaviour. In contrast, in a study of 681 subjects carried out in Lithuania, Aleksejuniene et al. (2002) could not document an association between psychosocial stress and periodontitis, although they reported that the disease did correlate with lifestyle factors.

Conclusions

As is evident from the present review of analytical epidemiologic studies of periodontitis, significant advances in our knowledge related to risk factors have occurred over the last decade. Infection by specific bacteria at high levels, cigarette smoking, and poorly controlled diabetes mellitus have been established as the major risk factors for periodontitis, while a number of emerging risk factors need to be investigated further.

To facilitate further research and increased understanding, the following points need to be considered:

1. There is a need to introduce a uniform definition of periodontitis to be used in epidemiologic studies, so that findings from different research groups are readily interpretable. This definition may involve a composite variable based on combinations of several signs of the disease, may be graded to reflect different severity levels, and/or may be age related.
2. Studies need to specifically address the distinction between factors responsible for the onset of periodontitis *versus* factors affecting its progression. Such information is essential in order to design and test effective preventive or therapeutic strategies on the population level.
3. There is a need for longitudinal prospective studies that address specific hypotheses emerging from the cross-sectional data. These studies must include established risk factors as covariates along with new exposures of interest.
4. Intervention studies, fulfilling the ''targeting'' step of the risk assessment process, are particularly warranted. Obvious candidates in this context are studies of elimination/suppression of specific microbiota, possibly through an immunization approach, as well as studies of the efficacy of smoking cessation interventions in the prevention and control of periodontal infections, as an alternative to the traditional anti-plaque/anti-bacterial approach. Ideally, such studies must have a randomized-controlled trial design.
5. The genetic determinants of susceptibility to periodontitis need to be investigated using novel approaches. It appears that the study of the effect of a single polymorphism at a time, with no regard to the obvious redundancy of all biological systems, is a rather narrow approach. Novel, comprehensive methods of studying genotypic characteristics with actual bearing on the host's phenotype need to be utilized.
6. Parallel to research of ''downstream'' causes of periodontitis, the effects of more traditional, ''upstream'' exposures, such as education or poverty, should not be overlooked.

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