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Review Article

Researching periodontitis: challenges and opportunities

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Abstract

Aim and Methods: The evidence-based approach, voted in January 2007 as one of the 15 most important medical advances in the last 166 years, has increasingly shaped medical practice and education. In this paper, we apply the evidence-based approach to evaluate the aetiology of periodontitis; for comparison, we provide a brief description of the evidence-based method applied to the study of cardiovascular disease aetiology. We then discuss the challenges and opportunities to enhance the evidence base for periodontitis aetiology.

Results and Conclusion: While evidence for medical treatments has mostly come from clinical trials, evidence for primary prevention in medicine has largely emerged from cohort studies evaluating disease risk factors. The high cost of conducting large cohort studies makes it challenging to fund these investigations, particularly for primary dental outcomes such as periodontitis. Studies of periodontitis outcomes integrated into larger ongoing cohorts provide one way to overcome this problem. Other potential barriers to the conduct of these studies include outcome definition, prevention of bias, data analysis, and the focus on teeth at risk (rather than people at risk) of the outcome. We analyse these questions and provide possible solutions. As many of these issues are generic to dentistry, possible solutions can improve the quality of future studies and the evidence base for primary prevention in dentistry.

Key words: cohort studies; epidemiologic methods; evidence-based dentistry; evidence-based medicine; periodontal diseases

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The evidence-based approach, voted in January 2007 as one of the 15 most important medical advances in the last 166 years (2007), has increasingly shaped medical practice and education. The evidence-based method has the science of epidemiology at its core, and stresses systematic observation, synthesis of best evidence, and integration of the best evidence into practice (1992). In this paper, we apply the evidence-based approach to evaluate the *aetiology* of periodontitis, as this knowledge provides the basis for primary prevention. Moreover, as primary prevention is directed towards the individual, we concentrate on the identification of individual-level risk factors of periodontitis (as opposed to tooth-level factors). For comparison, we provide a brief description of the evidence-based method applied to the study of cardiovascular disease aetiology. We then the discuss challenges and opportunities to enhance the evidence base for periodontitis aetiology.

Conflict of interest and source of funding statement

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Evidence Base for Medicine – the Example of Cardiovascular Disease

While evidence for *medical treatments* has mostly come from clinical trials, evidence for *primary prevention* has largely emerged from cohort studies evaluating disease risk factors. Possibly the most celebrated cohort study is the Framingham Heart Study. A search of those words in PubMed returned over 1500 articles, the first one of which appeared in the *American Journal of Public Health* in 1951 (Dawber et al. 1951). The study started in 1949 in Framingham, MA, with over 5000 participants (Dawber et al. 1951). The participants and their offspring are being followed up to this day. The Framingham Heart study quantified the risk of clinical factors, such as cholesterol, blood pressure, diabetes, and cardiovascular disease (Castelli 1984), supplementing clinical observation.

Another landmark study is the ongoing prospective follow-up of 35,000 male, British doctors since 1954 (Doll et al. 2005). The British doctors' study provided the evidence for the Surgeon General's report on smoking (Doll et al. 2005). Two other large cohort studies in the United States are the Nurses Health Study, which started in 1976 with about 100,000 women (Belanger et al. 1978), and the Health Professionals Follow-up Study (HPFS) with about 50,000 men, which began in 1986 (Colditz et al.

1991). Both studies are ongoing. The guidelines on healthy living and diet are strongly influenced by publications from the Nurses Health Study and the Health Professional's Follow-up Study (Krauss et al. 2000). Together, all these studies have yielded more than 2000 publications and have been instrumental in shaping medical practice, education, and policies and programmes to prevent disease in millions of people the world over.

Evidence Base for Dentistry – the example of risk factors of periodontitis

We applied the evidence-based approach to evaluate individual-level risk factors of periodontitis. A PubMed search using the following statement: ''Periodontal Diseases''[MAJR] and ''Longitudinal Studies''[MeSH] NOT implant AND risk factor returned 197 studies, dating back to 1989. Of these, 55 studies were longitudinal and had periodontitis or periodontal disease as an outcome in the title. On reviewing the abstracts and manuscripts, we excluded studies if only tooth-level data were reported in the results (15), the primary outcome was tooth loss (4), similar results from the same cohort were reported more than once (7), the design was not a cohort, or the primary outcome was not periodontitis (8).

There were 21 longitudinal studies with periodontitis as the outcome and at least one individual characteristic (such as age, sex, smoking, alcohol intake, socioeconomic status, or others) in the results. Two very similar publications (Jansson & Lavstedt 2002, Jansson et al. 2002) appearing in the same journal issue were considered to be one study. The first study was published in 1991 (Grbic et al. 1991) and the latest in 2006 (Merchant et al. 2006) (Table 1). Sample size ranged from 68 (Airila-Mansson et al. 2005) to >40,000 (Merchant et al. 2003a), follow-up 6 months (Grbic et al. 1991) to 26 years (Hashim et al. 2001, Baljoon et al. 2005), and loss to follow-up 0% (Grbic et al. 1991) to 68% (Neely et al. 2001). The median sample size was 394 (Ogawa et al. 2002). There was heterogeneity in the studies with respect to geography, socioeconomic status and ages of participants, duration of follow-up, quality of study, definition of outcome, and the exposures examined.

The cohort study is a relatively recent phenomenon in dentistry as compared with medicine. However, it is a particularly powerful study design because it makes it possible to evaluate potentially harmful exposures such as smoking or alcohol intake, or ubiquitous exposures such as air quality or diet, which would be unethical or impractical to assess using clinical trials. Because of its prospective nature, the study population is free of the disease under study at the outset when the exposure is measured, minimizing possibilities of recall bias. Recall bias is a particular concern in case–control studies because exposure assessment is made after development of the disease. The main problem with cross-sectional studies is that exposure and outcome are measured at the same time, and it is not possible to tell which came first. Mechanistic studies provide clues about disease aetiology but do not directly evaluate it. Information from cohort studies is thus invaluable to identify risk factors of disease, which form the basis for primary prevention recommendations. *There is no landmark cohort study of periodontitis risk factors like the Framingham Heart Study; hence, much of the information on its risk factors is based on results from smaller studies, cross-sectional data, and mechanistic studies, which yield a relatively lower level of evidence.*

Challenges to Conduct Cohort Studies with Periodontitis as an Outcome

Even though cohort studies provide the best evidence of disease risk factors, not many studies have been conducted to evaluate periodontitis risk factors. This section describes some of the potential reasons why this is the case (Table 2).

Cost

Cohort studies require baseline data collection on a large number of people, and complete, ongoing follow-up. Results from a cohort study lose validity with increasing loss to follow-up (Hennekens & Buring 1987). Maintaining complete follow-up necessitates a stable study population, core investigators, and staff. The massive amounts of data generated require a highly skilled team and resources for data processing and analysis. Cohort studies are expensive for these reasons.

Cohort studies also pose methodological challenges necessitating innovation. For instance, the Framingham Heart Study investigators used logistic regression for the first time in epidemiology (Wilson et al. 1980); later, they used pooled logistic regression to simulate the Cox proportional hazards model, which took a long time to run on old computers (D'Agostino et al. 1990). The Nurses and Health Professional's study investigators developed tools to measure diet using questionnaires (Willett et al. 1987), new methods to analyse nutrient data (Willett & Stampfer 1986), and correct for measurement error (Rosner et al. 1990). Recognizing these reasons, a review of the epidemiology of periodontitis conducted by The American Academy of Periodontology states, ''Only a few longitudinal studies on periodontitis have been conducted because of their inherent difficulties and expense.'' (Burt 2005) It may therefore be more efficient to conduct cohort studies evaluating periodontitis as a part of ongoing cohort studies evaluating other general health outcomes. Nine of the 21 studies in Table 1 were conducted as part of ongoing cohort studies. The loss to follow-up in these studies ranged from <2% to 33%, with a median loss to follow-up of <5%. By contrast, the loss to follow-up in cohort studies that were primarily ''dental'' ranged from 0% to 59%, with a median loss to follow-up of 23%.

Defining periodontitis

Clinically, damage to the periodontium is measured in mm of clinical attachment loss (CAL), pocket probing depth (PPD), or radiographic alveolar bone loss (ABL) at various tooth sites. These data are then clinically interpreted to conclude whether or not an individual has periodontitis. A major problem associated with the use of these parameters in epidemiologic studies is the lack of consensus on how to define periodontitis. Different studies used different measures of periodontal disease. Furthermore, there was a large variation in the threshold levels used in defining a periodontitis case, regardless of the measures used.

The American Academy of Periodontology report states, ''Determining the prevalence of periodontitis in the US population, seemingly a straightforward issue, in fact is complicated by the various case definitions used. If

Table 1. Prospective studies evaluating individual-level data with periodontitis as an outcome

Study	Sample size	Loss to follow-up (%)	Years of follow-up	Age of participants	Outcome	Main exposure/s
Grbic et al. (1991)	75	0%	6 months	32–69 years at baseline	⩾1 site with CAL 2.5+mm	Age, sex, marital status, education, occupation, health status, number of missing teeth, clinical periodontal parameters at baseline
Ship & Beck (1996)	95	Not stated	10 years	29–76 years	Change in mean CAL	Age, sex
Beck et al. (1997)	540	33	5 years	65+years at baseline	⩾3 mm CAL between visits	Education, dental visits, baseline periodontal parameters, microbiology
Baelum et al. (1997)	398	33	10 years	20–80 years at baseline	% sites with 2, 3, 4 mm CAL between examinations	Age, sex, CAL, PPD, plaque, calculus, BOP
Machtei et al. (1997a)	79	16	1 years	25–66 years	Mean CAL, ABL (change from baseline)	Smoking, cotinine, microbiological data, clinical periodontal parameters at baseline
Muller et al. (1997)	201	48	1 years	18–25 years at baseline	⩾1 site with increased PPD ⩾3 mm between examinations	Baseline periodontal and dental caries status, microbiology, smoking
Taylor et al. (1998)	362	Not stated	2 years	15–57 years at baseline	Bone score change	Age, diabetes, calculus, baseline bone score
Norderyd et al. (1999)	474	23	~ 17 years	20–60 years at baseline	ABL>20% between examinations	Age, education income, general health, smoking, % sites with supragingival plaque, gingival inflammation, PPD⩾4 mm)
Machtei et al. (1999)	985	49	2–5 years	25–75 years	PPD, CAL	Medical and dental history; socioeconomic profile, clinical measurements, microbial samples, and radiographic assessment of bone
Timmerman et al. (2000)	160	35	7 years	15–25 years at baseline	Presence of site with CAL⩾2 mm between visits	Age, sex, clinical, and microbiological parameters
Cullinan et al. (2001)	295	Not stated	5 years	18–65 years	PPD, CAL⩾2 mm between visits	IL-1 polymorphism
Neely et al. (2001)	154	68	20 years	14–31 years at baseline	Mean CAL	Age, gingival inflammation, calculus
Hashim et al. (2001)	914	<2	26 years	26 years	⩾1 site with 4 mm CAL	Smoking
Jansson et al. (2002)	513	54 I	20 years	35 years at baseline	Mean marginal bone loss from radiographs.	Smoking, age, sex, education, oral hygiene methods, baseline periodontal status, plaque index
Ogawa et al. (2002)	394	21	2 years	70 years at baseline	⩾1 sites with ⩾3 mm change in CAL from baseline	Smoking, baseline CAL, number of remaining teeth
Merchant et al. (2003a)	42,523	<5	4 years	40–75 years at baseline	Report of professionally diagnosed periodontitis	Anger expression, social support
Merchant et al. (2003b)	39,461	<5	14 years	40–75 years at baseline	Report of professionally diagnosed periodontitis	Physical activity
Pitiphat et al. (2003)	39,461	<5	14 years	40–75 years at baseline	Report of professionally diagnosed periodontitis	Alcohol intake
Airila-Mansson et al. (2005)	68	0	17 years	54 years on average	% bone height of baseline value	Smoking
Baljoon et al. (2005)	101	59	10 years	20–60 years at baseline	Change in the proportion of people having ⩾2 mm vertical ABL at second examination	Smoking
Merchant et al. (2006)	34,160	<5	14 years	40–75 years at baseline	Report of professionally diagnosed periodontitis	Whole grain intake

CAL, denotes clinical attachment loss; PPD, periodontal probing depth; ABL, alveolar bone loss; BOP, bleeding on probing.

periodontitis is defined as the identification of at least one site with CAL of ⩾2 mm, around 80% of all adults are affected, and around 90% of those aged 55–64. When the case definition is at least one site with CAL of ⩾4 mm, the prevalence in those aged 55–64 drops to around 50%. When it is CAL of ⩾6 mm, prevalence is <20%. Using pockets of ⩾4 mm as a case definition, 30% of adults had met that criterion on at least three to four teeth.'' (Burt 2005) The report continues to state, '' ... any prevalence data need the reference markers of the relevant case definition and the age group to which they apply'' (Burt 2005). A variety of periodontitis definitions have therefore appeared in the literature, posing particular challenges to readers.

Another issue that needs to be considered is the use of partial-mouth recording of clinical periodontal parameters. To reduce cost, many epidemiologic studies

Table 2. Challenges to conducting cohort studies with periodontitis as an outcome

Challenges to conduct cohort studies with periodontitis as an outcome
Cost
Long period of follow-up
Core investigators and staff
Resources for data processing and analysis
Defining periodontitis
Definition varies by age
Multiple definitions
Continuous *versus* dichotomous measures
Missing teeth
Teeth lost due to periodontitis not included in the definition of the disease
Data analysis
Correlated outcomes
Mathematical coupling
Incident *versus* prevalent disease
Studying genetic factors
Difficulty in identification of relevant polymorphisms
Conceptualization of periodontitis
Gram-negative infection with multiple potential causative organisms similar to pneumonia
Alternative model?

measured periodontitis on a subset of teeth (Ship & Beck 1996, Beck et al. 1997, Timmerman et al. 2000, Hashim et al. 2001) with the expectation that these measurements will be representative of the whole-mouth status. Although it has been shown to be valid in some situations (Mumghamba et al. 2004), the use of partial-mouth recording usually results in an underestimation of both the prevalence and the severity of periodontal disease (Fleiss et al. 1987). This could lead to an underestimation of periodontitis incidence, and a reduction of effect estimates associated with risk factors under investigation.

It is even more challenging for epidemiologists wishing to conduct prospective studies. A first principle of cohort studies is that disease risk factors need to be related to *incident cases* (Hennekens & Buring 1987). This means that prevalent cases of disease need to be excluded at baseline. Because periodontal damage is ubiquitous, most investigators have not excluded baseline cases (17/21 studies in Table 1). Instead, they have used the measure of change in CAL (or another measure of periodontal damage) between two examinations to define incident lesions of periodontitis. Studying the progression of disease is one way to deal with the problem, but it does not directly answer the question of which risk factors are associated with periodontitis among those free of the disease.

Missing teeth

Teeth that are lost during follow-up can be a source of bias because factors causing tooth loss could be the same factors that cause periodontitis (Merchant & Pitiphat 2002). Moreover, periodontitis is a leading cause of tooth loss in adults (Burt 2005). A definition of periodontitis that solely depends on clinical measures (such as change in CAL, PPD, or ABL using pre-existing radiographs) would misclassify the outcome. Statistical adjustment for tooth loss might not completely remove the bias (Merchant & Pitiphat 2002). Tooth loss due to periodontitis was not accounted for in 17/21 studies.

Data analysis

The strategy of analysing tooth-level variables raises issues in data analysis. Tu et al. (2002) identified mathematical coupling as a potential source of bias in correlation and regression estimates from studies with difference measures (such as difference in CAL or PPD from the start to the end of the study). They showed in a simulation study using randomly generated PPD data that using difference measures over time induced spurious relations between two groups even when there was no true underlying association (Tu et al. 2002). The primary reason for the bias is that the two measures are not independent. Using proportions does not remove the bias (Tu et al. 2002). The methods to avoid mathematical coupling are either to compute the mean level of that variable (such as mean CAL or PPD) and use the difference of the means as an outcome, or to use multilevel models (Tu et al. 2004a, b). Multilevel models allow the use of individual data points while accounting for the inherent correlation between the measures.

Among the studies published from 2000 onwards, 1/12 used multilevel modelling accounting for the correlated outcomes (Cullinan et al. 2001), 1/12 used a definition of 4+ mm AL at one or more site (Hashim et al. 2001), 1/12 used mean ABL (Jansson & Lavstedt 2002, Jansson et al. 2002), and 4/12 assessed periodontitis through self-report (Merchant et al. 2003a, b, 2006, Pitiphat et al. 2003) (Table 1). In the remaining 5/12 studies, investigators identified individuals with disease progression if the difference in baseline and follow-up values of certain parameters was above the predefined threshold. Among the earlier studies, 2/9 (Machtei et al. 1997a, Norderyd et al. 1999) used the mean value of the parameter, 1/9 used SUDAAN to account for correlated outcomes (Beck et al. 1997), and the remaining used differences in clinical measures from baseline. All the studies reviewed either used individual-level data or tried to use some methods to account for correlation between outcomes. The studies that compared baseline and follow-up measures (11/21), however, may be biased because of mathematical coupling.

Studying genetic factors

Periodontitis is determined by a complex interplay between microbial, environmental, and genetic factors. Growing evidence over the last decade has shown that periodontitis has important hereditary influences (Kinane & Hart 2003). A twin study suggests that genetic variants could explain approximately 50% of the variation of chronic periodontitis (Michalowicz et al. 2000). Gene polymorphisms, or variations in nucleotide sequences, are found in at least 1% of the population. Polymorphisms are associated with increased risk of common systemic conditions such as diabetes, cardiovascular disease, and rheumatoid arthritis. Most of the polymorphisms associated with periodontitis are related to inflammation but the results are conflicting, possibly due to variations in the environment or racial disequilibrium (Takashiba & Naruishi 2006).

Identifying the relevant polymorphisms for common, complex diseases such as periodontitis is a daunting challenge. This is mainly because each polymorphism only makes a small contribution to overall susceptibility but may predispose individuals to increased risk by interacting with other polymorphisms and environmental factors such as smoking. The human genome has about 10 million polymorphisms (Cargill et al. 1999). Determination of genetic polymorphisms that influence periodontitis, either directly or by interacting with other exposures, requires large-scale genetic analyses using as many target genes and subjects as practically possible, or a method to study the genome-wide association. An alternate

strategy could be to identify polymorphisms associated with hypothesized mechanisms leading to periodontitis. Polymorphisms associated with inflammation have been evaluated in relation to periodontitis, but this could be expanded to polymorphisms associated with glycaemic control for instance.

Conceptualization of periodontitis

Conceptualizing periodontitis as an infectious disease would focus research on its microbiology, and tooth-level factors, which could result in possible treatment. However, periodontitis does not exactly fit the mould of a classical infectious disease such as measles. Measles does not occur without the measles organism, and vaccination against it results in an immune response that prevents the disease. There are multiple organisms associated with periodontitis that are present in the periodontal spaces even in undiseased mouths, albeit in fewer numbers.

Periodontitis shares similarities with pneumonia. Pneumonia is an infection of the alveoli, distal airways, and interstitium of the lung caused by any one of many organisms (Marrie et al. 2006). The airways are constantly exposed to potentially harmful organisms but health is maintained by host immune response (Marrie et al. 2006). When the host immune response is weakened, by HIV infection for instance, the risk of pneumonia is increased (Vieira et al. 1983). Even among otherwise healthy persons, community-acquired pneumonia risk was increased with smoking, higher alcohol intake, higher body mass index (BMI), and with lower physical activity, and essential fatty acid intake (Baik et al. 2000). All these lifestyle factors are hypothesized to impact pneumonia risk through host immune responses.

Periodontitis is described as an irreversible, cumulative condition, initiated by bacteria but propagated by host factors (Kinane 2001). Salvi et al. (1997) proposed that poor oral hygiene and exogenous infection convert normal flora into pathological flora, which, together with host response, leads to a chain of events leading to inflammation and periodontal damage. They hypothesized that risk factors exerted their influence on periodontitis pathology mainly by altering the host response (Salvi et al. 1997). Page and Kornman (1997) summarized the pathogenesis of periodontitis in a model in which environmental and acquired risk factors, and genes modified the host response to microorganisms and caused disease. An extension of this conceptualization of periodontitis causation is described in Fig. 1. This model proposes that putative organisms associated with periodontitis cause tissue breakdown following impaired host immune response. For instance, diabetes is hypothesized to raise periodontitis risk by the deposition in the periodontium of advanced glycation end-products (AGE) (Lalla et al. 1998). AGEs produced in the hyperglycaemic state are deposited in the periodontium where they induce inflammation and oxidative stress, accelerating periodontal damage (Lalla et al. 1998). Raised BMI induces hyperglycaemia (Klein et al. 2004) and by the same mechanism increases periodontitis risk. Likewise, increased physical activity (Ekelund et al. 2005) and whole grain intake (Liu & Willett 2002) improve glucose metabolism and are inversely related to periodontitis risk (Saito et al. 2001, Merchant et al. 2003b, 2006). This is consistent with a recent review linking obesity with periodontitis through the inflammatory pathway (Pischon et al. 2007). Alcohol intake impairs neutrophil function and raises the risk of periodontitis (Pitiphat et al. 2003) and pneumonia (Baik et al. 2000). Chronic stress stimulates the hypothalamic–pituitary–adrenal axis, resulting in higher circulating corticosteroid, which leads to hyperglycaemia, and has been related to increased periodontitis risk (Merchant et al. 2003a). This model may also explain why the relation between oral hygiene and periodontitis risk is inconsistent (Merchant et al. 2002), and why all people who are exposed to putative organisms do not inevitably develop severe periodontitis.

Implications for Future Periodontal Research

The epidemiologic evidence of periodontitis aetiology suggests that individual-level factors may play a significant part in the *primary prevention* of periodontitis, but this question remains inadequately studied. In this vacuum of data, the old paradigm of clinical impression, experience, and understanding of basic mechanisms has shaped our thinking. To move forward, there is a need to obtain evidence from studies and develop a knowledge base. Having identified the challenges – practical and scientific we face in conducting these studies, we need to overcome them, because they are not insurmountable.

Cost

It may be prohibitively expensive to establish a prospective cohort to study periodontitis, but if research questions were evaluated as sub-studies of ongoing cohorts, the cost would be marginal, making them feasible. Indeed, 9/21 studies that evaluated periodontitis risk factors were part of ongoing cohort studies, which were originally assembled to identify other outcomes.

Defining periodontitis

The clinician's perspective of periodontitis is slightly different from the

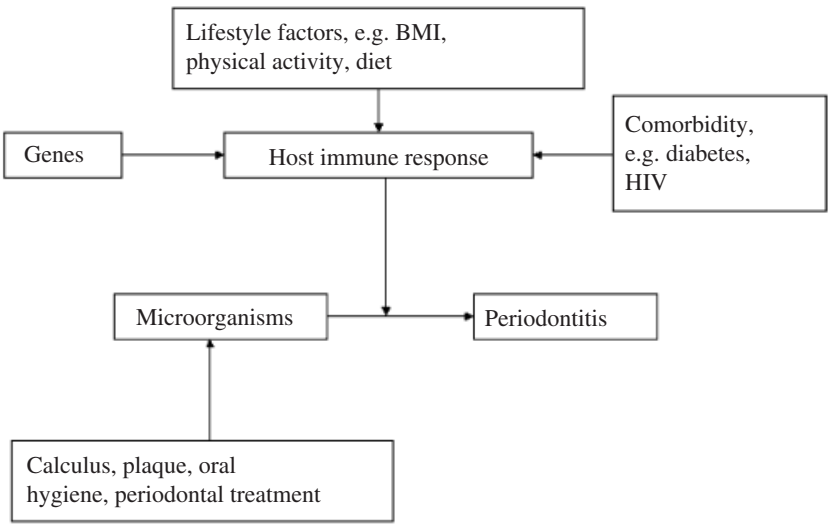

Fig. 1. Hypothesized model of periodontitis aetiology.

epidemiologist's. The clinician is primarily interested in current disease, while the epidemiologist usually wants to know whether an individual ever had periodontitis. Measuring CAL, PPD, or ABL (from pre-existing radiographs) on existing teeth provides information on current disease, its extent, and severity, and adequately meets the clinician's needs to plan treatment and monitor progress. Such a measure does not necessarily capture historical disease. For instance, a person with severe periodontal disease who lost many affected teeth could be classified as having no disease using CAL, PPD, or ABL measures. However, the epidemiologist would like to classify this individual as one with a history of disease because periodontitis is a cumulative condition (Kinane 2001). When teeth are missing that history of disease is lost. This missing information can lead to bias in epidemiologic studies. For example, consider a hypothetical cohort study evaluating fruit and vegetable intake and periodontitis risk. People with fewer teeth would be less likely to eat fruits and vegetables (Hung et al. 2003); if these people had lost teeth due to periodontitis then they would also be more likely to become incident cases in the study. Adjustment for teeth missing due to periodontitis at baseline would remove that bias (Merchant & Pitiphat 2002).

Moreover, epidemiologists prefer a dichotomous measure of periodontitis (rather than a continuous one) because the results of studies using a dichotomous outcome are easier to understand, and therefore more meaningful in clinical and public health settings (Borrell et al. 2006). Use of a dichotomous periodontitis measure makes it is possible to exclude persons with the condition at baseline. We suggest that baseline cases should be excluded using the same definition used to identify incident cases. For instance, suppose the case definition of periodontitis in a study is someone with at least four sites with 4 mm or more of radiographic bone loss. In this study, all participants at baseline who meet these criteria would be excluded before follow-up. The cases of periodontitis observed during follow-up would be new cases among a population free of disease (as defined by the investigators) at the outset.

Some investigators have combined information from CAL and PPD to derive a dichotomous measure of current and cumulative periodontitis (Borrell et al. 2006). This measure, however, does not capture teeth lost due to periodontitis, which can induce confounding in epidemiologic studies (Merchant & Pitiphat 2002). In the HPFS investigators determined periodontitis by asking the participants whether they had ever been professionally diagnosed with periodontitis. They further showed that responses to this question correlated well with radiographic measures of periodontitis (Joshipura et al. 2001). This is a dichotomous measure that captures periodontitis and tooth loss associated with it, but it may not be generalizable to other populations. More than half of the HPFS participants are dentists and the others are pharmacists, osteopathic physicians, optometrists, and veterinarians. Self-report to assess periodontitis in the general population is not as sensitive (Blicher et al. 2005). Pre-existing radiographs are a particularly attractive method to assess periodontitis in epidemiologic studies because they are easy to take, often routinely available, time specific, can be evaluated at any time without the participant being present (Merchant et al. 2004), and correlate well with other clinical measures such as CAL and PPD (Machtei et al. 1993, 1997b). A possible avenue for future research is the development of a composite measure of periodontitis combining information from a radiograph (or clinical measures if these are readily available) and self-report.

There is need for a consensus on the definition or definitions of periodontitis in epidemiologic studies so that the results from different studies can be comparable. It can also allay doubts about whether a particular definition was chosen after analysing the data or whether it was defined a priori. Leadership from epidemiologists working in the area of periodontitis can resolve this issue.

Data analysis

The two main issues in data analysis arising with the use of continuous measures of CAL, PPD, or ABL, with potential to cause bias, are correlated outcomes and mathematical coupling (Tu et al. 2002). Multilevel modelling, which is increasingly used in dental research, can remove bias from both these sources. However, such a study with a continuous measure still evaluates *prevalent* periodontitis; results from studies of prevalent periodontitis reflect factors related both to periodontitis aetiology and its progression. Previous studies using change in continuous measures as an outcome tend to report that existing periodontitis predicts future disease risk (Baelum et al. 1997, Beck et al. 1997, Machtei et al. 1997a, b, Muller et al. 1997, Taylor et al. 1998, Norderyd et al. 1999, Timmerman et al. 2000), or that treatment for periodontitis decreases future disease risk (Beck et al. 1997). While these findings are generalizable to people with existing periodontitis, they are not necessarily applicable to a population free of disease. Furthermore, in the evaluation of risk factors using prevalent cases, it is not clear whether factors such as age and smoking are related to new disease or its progression. As the distinction between prevalent and incident cases is not always clear in the existing studies of periodontitis, we need to remember this while interpreting them.

A standard, dichotomous definition of periodontitis addresses many issues in data analysis. It avoids bias arising from mathematical coupling and correlated outcomes because it is a single measure. By excluding prevalent cases at baseline, it is possible to evaluate incident cases in cohort studies.

Studying genetic factors

As periodontitis is a multifactorial disease, we need to explore candidate genes beyond the inflammatory pathway. As most of the prevalent polymorphisms by themselves are weakly associated with disease, it is necessary to evaluate them in relation to interactions with the environment. This strategy necessitates the conduct of large studies with large contrasts in the environment. Rapid improvements in genotyping technology and the completion of the International HapMap Project of the human genome (2005) have paved the way for genome-wide association studies, in which a set of polymorphisms across the genome is genotyped to identify the multiple genetic variations contributing to the disease. Although such methods offer great promise in our understanding of disease, their application to periodontal research imposes further methodological and financial challenges.

Conceptualization of periodontitis

The proposed model of periodontitis aetiology is a hypothesis that needs to be tested in studies. It was inspired

by the observation that improved glycaemic control in type II diabetics reduced periodontitis risk (Grossi & Genco 1998, Taylor et al. 1998, Tezal et al. 2006). As glyceamia is a continuous variable, and varies substantially even among non-diabetic individuals (Muntner et al. 2004), we hypothesized that factors affecting it may also alter periodontitis risk. Hyperglycaemia is positively associated with adiposity, and negatively with physical activity (Abuissa et al. 2005) and whole grain intake in non-diabetic individuals (Liu & Willett 2002). A positive association between adiposity and periodontitis risk had been reported in the literature at that time. We therefore evaluated physical activity and whole grain intake, and consistent with our hypothesis, found it to be inversely related with periodontitis risk even among individuals without diabetes. An evaluation of risk factors associated with pneumonia – another relatively common infection caused by multiple organisms – reinforced the idea that lifestyle factors may play a role in periodontitis prevention.

Lifestyle choices – such as diet, physical activity, smoking, and alcohol intake – impact many of the mechanisms that can alter glycaemia and immune function. Moreover, they are potentially modifiable. A clearer understanding of their role in periodontitis aetiology will help us understand why periodontitis occurs in some people but not others, and what we can tell individuals to do to prevent it. But to be able to do that, we need to conduct the studies, overcome the methodological, financial, and conceptual challenges, and in doing so, expand the evidence base for dentistry.

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Clinical Relevance

Scientific rationale for the study: Longitudinal studies provide scientific evidence for primary prevention, but many prospective studies evaluating periodontitis aetiology find that existing periodontal lesions predict future disease. There is little advice dentists can give for primary prevention of periodontitis based on current evidence.

Principal findings: We found that many studies of periodontitis aetiology were conducted with prevalent periodontitis mainly because of the difficulty in defining disease. The other issue was differentiating between tooth- and person-level data. This was evident in data analysis and conceptualizing the research question.

Practical implications: For primary periodontitis prevention, we need to focus on person-level factors.