Associations Between Periodontal Disease and Systemic Disease: Evaluating the Strength of the Evidence

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Much work has been published on the association between periodontal disease and systemic disease, including original reports, narrative reviews, systematic reviews, and meta-analyses. Based on the existent work, one can assign an evidence level and grade, using standard evidence-based criteria, to the data available in the four major categories of medical outcomes studied: cardiovascular/cerebrovascular, pregnancy, pulmonary, and diabetes. We discuss methodologic and conceptual problems in the study of oral-systemic associations, focusing as an example on the association between periodontal disease and cardiovascular/cerebrovascular disease. We argue that the hierarchical ranking of studies by levels of evidence may be misleading. In particular, while randomized controlled trials (RCTs) are needed to determine the efficacy of periodontal treatment to reduce the risk of cardiovascular events, they may be of limited value in determining the etiologic role of periodontal disease on coronary heart disease and stroke. We discuss limitations of RCTs as well as the limitations of currently available data from epidemiologic studies, including study design and confounding and misclassification errors. We conclude that well-designed observational studies into the associations between periodontal disease and systemic disease need to remain an integral component of future research efforts in order to fully understand such associations. J Periodontol 2005;76:2175-2184.

KEY WORDS
Cerebrovascular disease; coronary heart disease; epidemiologic studies; periodontal disease; randomized controlled trials; stroke.

The possible role of periodontal infections in the pathogenesis of systemic diseases remains an important but unresolved question. These symposium presentations highlight the breadth and depth of interest on this topic. In less than a decade, there has been extraordinary growth in the evidence base, including laboratory, animal, and human studies, on the relation between periodontal disease and important systemic health outcomes. Furthermore, a number of systematic reviews and meta-analyses on specific oral-systemic associations have been published.1-7

We will focus here on some methodological issues that are important in evaluating clinical epidemiologic research and in guiding plans for randomized controlled trials. We will focus on the association between periodontal disease and coronary heart disease (CHD) and ischemic stroke. However, many of the points made apply to the other systemic health outcomes under study.

CAUSAL THINKING VERSUS LEVELS OF EVIDENCE
A key question is whether periodontitis is a causal factor in the etiology of CHD and/or stroke. Much epidemiologic research is devoted to the estimation of causal effects using non-experimental data. Unfortunately, the results of epidemiologic studies, typically yielding a measure of association, are insufficient to conclude whether such associations are causal. The correct interpretation of
statistical associations between periodontal disease and CHD depend on a variety of issues, including but not limited to, confounding bias, other sources of bias, and chance.

Several criteria have been suggested for evaluating the likelihood that exposure–disease associations in observational studies are causal. Such criteria, in particular the Bradford Hill criteria, have been previously applied and discussed in the context of the periodontal disease–cardiovascular disease association. It is well recognized that the application of these criteria, while suitable to guide one’s thinking, will not provide a definitive answer. The limitations of these criteria are many and have led some to propose the term causal “values” rather than causal “criteria.”

Hence, conclusions reached by weighting the available evidence by different researchers may differ. In an attempt to evaluate and quantify this “conclusion-making” process, Holman et al. conducted a psychometric experiment on causal inference among epidemiologists who were asked to decide whether to attribute causality to 12 summaries of evidence concerning a disease and a chemical exposure. Factors with the strongest influence on the odds of causal attribution were statistical significance; refutation of alternative explanations; strength of association; and adjunct information concerning biological, factual, and theoretical coherence; and the number of supportive studies. The results demonstrate that in epidemiologic practice, conclusions are reached by weighing evidence from several sources and not merely by combining the quantitative results of clinical studies. Causal criteria are inevitably applied by epidemiologists and clinical researchers, formally or informally, on an everyday basis. However, in the absence of experimental evidence from randomized controlled trials (RCTs), the determination of an observed association as causal is neither truly objective nor easy. As Kaufman and Poole noted, “no final resolution has emerged to the challenges of thinking about causes and their effects or to the formidable task of forming causal judgments about relations between variables.”

These concerns also apply directly to the current status of work on periodontal-systemic associations. In the era of evidence-based medicine (EBM), it is only natural for a clinical scientist to feel somewhat uncomfortable with such subjective criteria. With the advent of EBM, a ranking system based on levels of evidence has been developed (Table 1). It is important to note that the concept of EBM was originally developed to evaluate interventions, rather than to address etiologic research questions per se. However, the Oxford Centre for Evidence-Based Medicine Levels of Evidence now specifically include “Etiology” as a category.

Using such EBM criteria, we could assign an evidence level and grade to the work in the four major categories of medical outcomes studied: cardiovascular, pregnancy, pulmonary, and diabetes outcomes (Table 1). For example, in regards to the periodontal disease–cardiovascular association, the highest evidence level that can be assigned is 2b, with a grade of B, based on the existence of several but inconsistent cohort studies. To achieve an evidence level of 1 and a grade of A, there would at minimum need to exist more than one high-quality definitive RCT.

It becomes clear from the EBM levels of evidence criteria that all that can be done to improve the evidence rating is to conduct RCTs. In a field where narrative (i.e., non-systematic) reviews and opinion papers still outnumber original research contributions (for the past 5 years, the ratio is approximately 1.3:1), and where the exposure of interest is a disease that can be successfully treated in a majority of patients, observational studies may be regarded to provide little additional value and RCTs considered to be required to provide definitive answers. Indeed, it has been suggested that “in order to elucidate whether the relationship between cardiovascular and periodontal disease is causal in nature we need data from controlled intervention trials rather than observational studies.”

### Levels of Evidence for Etiologic Studies as Proposed by Oxford Centre of Evidence-Based Medicine

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| 1     | a SR with homogeneity of RCT  
|       | b Individual RCT with narrow confidence interval  
|       | c All or none |
| 2     | a SR with homogeneity of cohort studies  
|       | b Individual cohort study (including low quality RCT; e.g., <80% follow-up)  
|       | c “Outcomes” research; ecological studies |
| 3     | a SR with homogeneity of case-control studies  
|       | b Individual case-control study |
| 4     | Case series and poor quality cohort and case-control studies |
| 5     | Expert opinion without explicit critical appraisal, or based on physiology, bench research, or “first principles” |

“Grades of Recommendation” are assigned as follows: (A) - consistent level 1 studies; (B) consistent level 2 or 3 studies or extrapolations from level 1 studies; (C) level 4 studies or extrapolations from level 2 or 3 studies; (D) level 5 evidence or troublingly inconsistent or inconclusive studies of any level, SR, systematic review.
However, we argue that while RCTs are needed and will provide important clinical knowledge, they may not necessarily answer the question whether periodontal disease is causally related to CHD/stroke. Furthermore, we believe that well-designed observational studies, including case-control studies, remain necessary to adequately evaluate the association between periodontal disease and CHD/stroke. The ranking of etiologic studies based on evidence levels that were originally developed to evaluate the evidence for interventions may be misleading if one concludes that RCTs are the best way to answer to an etiologic question, or even a better way than using observational studies. For example, our understanding and acceptance of tobacco smoking as a major etiologic factor in various systemic diseases did not come from RCTs, but rather from the accumulating weight of epidemiologic data over many decades. In fact, it would be unethical and impractical to conduct an RCT that could directly answer an etiologic question on tobacco’s health effects.

**LIMITATIONS OF RCTs**

There are important limitations in the use of RCTs, as well as limitations in the use of observational studies, when evaluating the association between periodontal disease and CHD/stroke. RCTs are extremely powerful in that they can provide definitive answers as to whether a specific intervention “works”; i.e., whether it has a desired or expected effect of a certain size. In large RCTs, randomization at least theoretically assures even distribution of all factors (i.e., known and unknown confounders) so that differences in the outcome must be attributable to the intervention.

However, in practice, deviations from an “ideal” RCT inevitably occur. Loss to follow-up, masking, and non-compliance issues may hamper the validity of RCTs. In addition to these methodological problems, RCTs may not be feasible because of logistic, ethical, or financial reasons. All of these issues may be relevant to RCTs aimed at investigating the periodontal disease–CHD/stroke relationship. For example, since CHD/stroke events may take years to occur, loss to follow-up and non-compliance could be high in such studies. These may remain important issues even in secondary prevention trials. Furthermore, subjects need to meet both cardiovascular and periodontal inclusion criteria. A recently completed RCT on the effect of periodontal therapy on metabolic control of diabetes mellitus among veterans screened 2,534 subjects in order to randomize 193 subjects, and 166 (86%) of them completed this 12-month trial. However, work in this area is ongoing and it is expected that such methodologic and practical concerns can be successfully addressed despite the many challenges.

Apart from methodological, logistic, financial, and ethical caveats, some questions simply cannot be studied in RCTs. Strictly speaking, the question whether periodontitis causes CHD/stroke is such a question, because periodontitis cannot be randomly assigned to human subjects, and not just for ethical reasons. At best, for example, an RCT on periodontal therapy for the secondary prevention of stroke that finds a protective effect of therapy will provide strong, but still only indirect, evidence that periodontal disease causes stroke. Perhaps more importantly, a negative result from such a trial would signify only that the specific intervention tested was not effective in the specific patient group investigated. Such negative intervention results would really tell us little about whether periodontal disease causes stroke.

Recently, the results were reported from two major cardiovascular RCTs on the efficacy of antibiotic treatment directed at *Chlamydia pneumoniae* for the secondary prevention of coronary heart disease and stroke. In the antibiotic arm of the PROVE-IT trial, patients with an acute coronary syndrome were randomized to receive either placebo (N = 2,086) or monthly courses of gatifloxacin (N = 2,076), which is bactericidal for *C. pneumoniae*. Patients were followed for 2 years, using a composite primary endpoint (death, myocardial infarction, documented unstable angina requiring hospitalization, revascularization, or stroke). The 2-year cumulative incidence of the primary endpoint was similar in both groups (placebo: 25.1%; treatment: 23.7%). Interestingly, results were similar for patients with baseline concentrations of C-reactive protein above the median (placebo: 24.9%; treatment: 25.2%) and below the median (placebo: 21.6%; treatment: 24.4%). Furthermore, in secondary analyses, no particular subgroup could be identified in which the treatment was effective. The authors concluded that long-term antibiotic treatment directed at *C. pneumoniae* is not able to reduce the risk of recurrent cardiac events.

A separate large RCT randomized patients with documented stable coronary artery disease to either placebo (N = 2,008) or 600 mg azithromycin once per week for a year (N = 2,004). Patients were followed for up to 4.5 years using a composite primary endpoint (fatal myocardial infarction, coronary revascularization procedure, hospitalization for unstable angina). The cumulative incidence in both groups was identical (placebo: 22.4%; treatment: 22.3%). The authors concluded that there is no clinically significant benefit in the secondary prevention of coronary heart disease events from 1 year of weekly azithromycin treatment, and that neither *Chlamydia pneumoniae* nor another organism susceptible to azithromycin plays an important role in the pathogenesis of coronary events in subjects with advanced CHD.
What are possible explanations for these (disappointing) results? One is simply that infections do not play any important causal role in the pathogenesis of atherosclerosis, or more specifically that the associations between C. pneumoniae infection and atherosclerosis found in observational studies are not causal. However, many other equally plausible alternative explanations may be given, including, but not limited to, concerns that the selected antibiotics may not have been effective for all relevant microbiota or that infections may only be causally important in the early stages of atherogenesis. In any case, the negative results of these large “definitive” RCTs may have put the nail in the coffin for antibiotic strategies for the secondary prevention of cardiovascular events, but do not rule out a causal role of C. pneumoniae in atherogenesis. Similarly, negative findings in RCTs of periodontal therapy for the secondary prevention of cardiovascular outcomes would not necessarily mean that periodontitis has no causal role in atherogenesis, nor would such results imply that prevention of periodontitis has no effect on cardiovascular disease incidence. Again, the key point is that RCTs can provide definitive answers on the efficacy of specific interventions, but cannot necessarily answer causal questions of disease etiology.

**CURRENT EVIDENCE FROM OBSERVATIONAL STUDIES**

The ranking of studies based on the EBM levels of evidence (Table 1) is unsatisfactory when applied to etiologic research questions for another important reason. The EBM scheme is based on general study design criteria, but the specific characteristics of the individual studies and their research questions are not specifically taken into account. In reviewing published studies on the association between periodontitis and coronary heart disease/stroke, issues such as exposure misclassification and confounding may be more important than study design (i.e., whether case-control, prospective cohort, etc.).

Cohort studies are frequently considered superior to case-control studies, and this perception is reflected in the EBM levels of evidence, where cohort studies yield level 2 evidence while case-control studies yield level 3 evidence. This ranking suggests that, by their nature, case-control studies are inherently inferior to cohort studies. Given that there already is level 2 evidence for the association of periodontal disease and coronary heart disease/stroke, should we conclude that conducting further case-control studies would be a waste of time and money?

It has been stated that the poor reputation of case-control studies "stems more from instances of poor conduct and overinterpretation of results than from any inherent weakness in the approach." Indeed, case-control studies may be conceptualized as a more efficient type of cohort study. For example, the estimates derived from a nested case-control study, where cases and controls are selected from a defined cohort of subjects, would not be expected to differ from estimates derived from the underlying cohort study, although the case-control approach may be more cost-efficient. More generally, any case-control study can be thought of as being nested within the source population.

A related but different issue is the distinction between prospective and retrospective studies, the former usually being considered superior to the latter. However, such judgment is groundless without considering the specifics of the particular study. The terms prospective and retrospective usually refer to the time of exposure/covariate assessment relative to disease occurrence. The accurate assessment of exposure and outcome measurements as well as covariates is a prerequisite for valid inferences from observational studies, as measurement error or misclassification will introduce bias. It makes intuitive sense that for certain exposures and outcomes, these measurements can be more accurate if they are made in an on-time fashion, rather than retrospectively (e.g., from records or patients’ recall). However, for some exposures, this may be less important.

The above-noted concerns directly apply to evaluating current evidence on the relationship between periodontal disease and CHD/stroke. For example, in a recent case-control study on the association of periodontitis and stroke, radiographic measures of bone loss and clinical measurements of attachment loss are accurate cumulative measures of history of periodontitis. This may not hold for clinical measures of gingivitis, as gingival inflammation measured days after occurrence of a stroke may be very different from the average gingival inflammation existent prior to the stroke. Hence, retrospective case-control studies of the association between periodontitis and CHD/stroke may be very valuable, while the interpretation of findings related to gingivitis may be more problematic.

So, what may we conclude from a review of the evidence from studies with the highest level of evidence? A recently published meta-analysis of cohort studies of the association between periodontal disease and risk of CHD/stroke included nine reports of cohort studies. The majority of these reports were of prospective cohort studies; i.e., the assessment of periodontal disease was made prior to the occurrence of the events of interest. The summary relative risk found in the meta-analysis was 1.19 (95% CI: 1.08 to 1.32), indicating a small but significant association between periodontal disease and CHD/stroke. Three of the reports actually represented different analyses...
of the same cohort (NHANES I Epidemiologic Follow-Up Study).29-31

Four studies used Russell’s periodontal index (PI) to assess periodontal disease, an index that relies on a visual examination of the periodontium rather than periodontal probing.29-32 Two studies, which were conducted on physicians and other health professionals, used subjects’ self-report to ascertain periodontal disease status.33,34 One study is published as an abstract only.35 Only this latter study and one other study actually used a quantitative measure of periodontal disease history (alveolar bone loss) for exposure assessment.9 We identified two additional publications relating to prospective cohort studies that were published later. In a study from Finland, periodontal status was assessed using a crude clinical index on a per quadrant basis that categorized subjects based on the presence of any pocket 4 to 6 mm or deeper than 6 mm.36 Another study reported on the association between self-reported periodontal disease history and ischemic stroke among U.S. health professionals.37 Hence, misclassification of periodontal disease status, which can be reasonably assumed to be non-differential, is likely a major problem in the majority of the currently available cohort studies. Typically, the main effect of such non-differential misclassification is attenuation of the effect measure; i.e., the relative risk will be closer to 1. Such attenuation can be quite dramatic.38-40

To illustrate this point regarding periodontal measures, we conducted a simple simulation study (Table 2; T. Dietrich, R. Garcia, unpublished data). A similar approach has been employed previously to study the effect of self-report of smoking on residual confounding.41 We used data on periodontal attachment loss and probing depths of mesio-buccal sites from 12,976 subjects in NHANES III. From this population, we sampled with replacement samples of size N = 5,000 and calculated times to fictional morbid events (which depends on the threshold used to define it), and the strength of the association (i.e., the true RR).38 It is important to note that misclassification of periodontal disease could therefore also bias the assessment of the effect of age or gender on the periodontal disease–CHD/stroke association, as the prevalence of periodontal disease differs between such groups.38,48 For example, let us suppose a true RR of 4.0 for young subjects and 1.5 for old subjects. Further, let us assume a misclassification with sensitivity of 70% and specificity of 90%, and a prevalence of periodontal disease of 1% and 10% among young and old subjects, respectively. The relative risk estimate for both groups would calculate as approximately 1.2, completely masking the differential effects of the periodontal disease among different age groups.

In their meta-analysis, Janket et al. demonstrated that the type of periodontal disease assessment explained some of the heterogeneity between studies.3
It is, therefore, reasonable to assume that, if, indeed, an independent association between periodontal disease and CHD/stroke exists, this association may in fact be stronger than suggested by the currently available cohort studies.

It is also worth mentioning that the term “prospective” has not been consistently used to refer to the order of exposure/covariate and outcome assessment. In a systematic review of studies relating periodontal disease to CHD/stroke, Scannapieco et al. state that “to date, results from a prospective, longitudinal epidemiologic study have not been reported.”

This statement presumably refers to the fact that results from a cohort study specifically designed to evaluate the association between periodontal disease and CHD/stroke are not available. However, it is noteworthy that this is not a limitation in the sense that inferences from “secondary analyses” of existing data are not, per se, valid. Primary hypotheses and primary endpoints may be important in a clinical trial setting; they have little bearing in observational epidemiologic studies. Rather, the choice of the study population and the methods employed to measure exposure, outcome, and covariates may be more appropriate for a specific research question if the study was designed to evaluate this question. By the same token, larger studies are usually more precise; i.e., produce narrower confidence intervals, but are not necessarily more valid than smaller studies. Again, the assessment of exposure, outcome, and covariates are key factors, and often better measurements can be made with more accurate methods in smaller studies.

One recently published case-control study on the association between periodontal disease and ischemic stroke exemplifies how a carefully planned and executed case-control study can provide new and important evidence. The study was conducted in one German university hospital and recruited 303 incident cases of acute cerebrovascular ischemia, 300 population controls, and 168 hospital controls. Periodontal status was assessed in a comprehensive oral examination including periodontal probing at four sites in all teeth. Subjects were categorized into four categories based on mean clinical attachment levels (CAL),

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* Sensitivity of diagnosis = true positive diagnoses/actual cases.
† Specificity of diagnosis = true negative diagnoses/actual non-cases.
‡ ≥1 mesio-buccal site with PD ≥4 mm, prevalence of disease = 29%.
§ ≥4 mesio-buccal sites with PD ≥4 mm, prevalence of disease = 5.3%.
‖ ≥1 mesio-buccal site with PD ≥6 mm, prevalence of disease = 4.7%.

Table 2.

Hazard Ratios, 95% Confidence Intervals, and Relative Bias for the Association Between Periodontal Disease and a Hypothetical Event for Different Degrees of Misclassification of Periodontal Disease.
which allowed evaluation of a dose-response pattern. The study found a strong association between history of periodontitis and the incidence of acute cerebrovascular ischemia. Compared to subjects with mean CAL less than 3 mm, the odds ratio (OR) for subjects with CAL 4.5 to ≤6 mm was 2.7 (95% CI: 1.4 to 5.3), and for subjects with CAL >6 mm the OR was 4.3 (95% CI: 1.8 to 10.2). Furthermore, results of stratified analyses suggested that the association was stronger in younger subjects and in males (Fig. 1). Hence, the study supports the hypothesis that the association between periodontal disease and cardiovascular disease may be stronger in younger subjects, as previously reported, and suggests that the association may be stronger in males. However, the study was not designed to evaluate such effect modification and the power of these subgroup analyses is limited.

A large multicenter case-control study would allow evaluating the association in different subgroups in an efficient manner. Such findings may not only contribute to our understanding of the periodontal disease–cardiovascular disease association, but also have important implications in regards to the design of intervention studies. For example, if the association between periodontitis and stroke was, in fact, very small or absent in older subjects, the rationale for an intervention study for the secondary prevention of cerebrovascular events in older subjects would have to be questioned.

**CONFOUNDING**

Confounding is an important issue that invariably arises when causal effects are estimated from non-experimental data. In the case of the periodontal disease–cardiovascular disease association, confounding arises from risk factors for cardiovascular disease that are independently associated with periodontal disease. The amount of bias introduced by a confounding variable depends on the strength of the association with both periodontal disease and cardiovascular disease as well as the prevalence of the confounding variable in the study population. Smoking is an established risk factor for CHD and stroke. It is also an established risk factor for periodontal disease. Furthermore, cigarette smoking is a relatively common exposure. Therefore, smoking is a very important confounding variable in the association of periodontal disease and cardiovascular disease. Even if smoking is adjusted for in the statistical analysis, residual confounding by smoking history is of great concern, particularly since the reported associations between periodontal disease and CHD/stroke are small.

The role of smoking as a confounder of the oral health–systemic disease association is receiving increasing attention. One possible source of residual confounding by smoking is the measurement error associated with self-reported smoking measures. However, even if smoking history could be accurately measured, modeling smoking history in statistical models is not straightforward, as smoking is a multi-dimensional phenomenon with various characteristics like intensity, duration and time since cessation. Hence, another possible source of residual confounding is the categorization of continuous smoking characteristics like intensity or duration.

These inherent difficulties in assessing all dimensions of cigarette smoking and the inability to completely account for them in statistical models have led some authors to suggest the restriction of studies on periodontal disease–CHD/stroke associations to never smokers to avoid residual confounding. However, this goal may be difficult to achieve for practical reasons. More importantly, effect modification by smoking is an alternative explanation if an exposure–disease association can only be demonstrated in smokers and results found among never-smokers may not be generalizable to smokers. It may be difficult to decide between residual confounding and effect modification in specific analyses. Unfortunately, the currently available biomarkers are of limited value for assessment of smoking history in epidemiologic studies on the association between periodontal disease and CHD/stroke. Biomarkers such as cotinine can confirm that a subject is currently non-smoking and correlate with smoking intensity in current smokers. However, they do not provide information on smoking duration nor are they useful to assess smoking history in former smokers. In countries where the smoking epidemic passed its peak years ago, such as the United States, the proportion of former smokers among ever smokers has risen constantly and former smokers constitute an important

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**Figure 1.** The association between history of periodontitis and acute cerebral ischemia; results from a case-control study. Adjusted OR for all subjects (red squares) by mean CAL and stratified by age (blue diamonds) and gender (green triangles).
population in clinical research. This is particularly relevant in studies of older adults, where, in addition to the overall decline in smoking, the increased mortality among smokers contributes to the higher proportion of former smokers. This age-dependent rise in the proportion of former smokers among ever smokers has been demonstrated in a series of representative surveys between 1980 and 1992.64

Hence, effect estimates should be reported separately for never smokers, which will convey important additional information. However, statistical methods that make efficient use of the information collected on smoking history are desirable. We have recently proposed a comprehensive smoking index that simultaneously accounts for intensity, duration, and time since cessation for former smokers.65 This index can also account for changes in smoking intensity over time which is usually ignored in analyses. Such approaches may also be useful to reduce residual confounding by smoking history. Importantly, in their meta-analysis of available cohort studies, Janket et al. identified residual confounding as a source of heterogeneity between studies.3 Hence, residual confounding may explain the small associations found in the available cohort studies.

CONCLUSIONS
The currently available evidence from epidemiologic studies suggests that there is a significant, although modest, association between periodontal disease and coronary heart disease and other systemic health outcomes. However, there is concern that this association may be due to confounding by smoking or other, unknown factors. In contrast, misclassification of the periodontal exposure may attenuate the strength of the observed relationship. The currently available data from observational studies are insufficient to accurately estimate the strength of the association. RCTs to evaluate the effect of periodontal therapy in patients with chronic periodontitis on inflammatory biomarkers, other cardiovascular risk factors, and ultimately on risk of cardiovascular events, are desirable and important. However, such RCTs may not yield a definitive answer as to whether periodontal disease is causally related to coronary heart disease/stroke or any other systemic health outcome. There will remain a need for well-designed, carefully analyzed, and correctly interpreted observational studies, including case-control-studies, in order to adequately understand the association between periodontal disease and systemic disease in various populations.

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