Challenges in interpreting study results
The conflict between appearance and reality

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As noted in the articles in this supplement, a large body of evidence to date suggesting a possible association between oral and systemic diseases consists of epidemiologic (observational) studies. Although the results of such studies at times have been interpreted as indicating a causal relationship between diseases, it is important to recognize that epidemiologic studies have inherent limitations that preclude establishing causal relationships. The aim of this article is to help readers understand some of the strengths and limitations of epidemiology so that they can better interpret studies of periodontal and systemic diseases. In addition, it will briefly consider types of studies that can build on the epidemiologic data to provide more definitive answers to questions of causality.

THE CONCEPT OF ASSOCIATION VERSUS CAUSALITY

The finding of a statistically significant relationship between two or more diseases or factors in an epidemiologic study can be due to one of several possibilities:

- the two diseases or factors may

ABSTRACT

Background. Many studies investigating the relationship between periodontal disease and systemic diseases have been reported; the majority of these have been epidemiologic (or observational) studies. The purpose of this article is to help readers understand the strengths and limitations of epidemiology for the purpose of being better able to interpret these studies.

Findings. Epidemiologic studies include retrospective case-control studies and prospective cohort studies. While these studies cannot prove causality, they can provide strong evidence for and show the strength of an association between a disease and putative causative factors. Randomized controlled trials (RCTs) are used to test therapeutic and preventive measures and can provide presumptive evidence of disease causation in certain circumstances. Each of these study types has limitations that can distort the study results and, therefore, should be considered in study design and analysis.

Conclusions and Clinical Implications. Epidemiologic studies conducted to date suggest an association between periodontal disease and a number of systemic diseases. However, the strength and nature of this association are not yet clear, because in some cases it might result from confounding by smoking or other variables. Additional well-designed observational studies and future RCTs should increase our understanding of the actual relationship between periodontal and systemic diseases.

Key Words. Epidemiology; case-control studies; cohort studies; disease causation.

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have occurred coincidentally in the specific population studied, thus producing an apparent association between the two;
- the two diseases may have resulted from the presence of a risk factor common to both in the population, also producing an apparent association between the two;
- the two diseases may, in fact, have a causal relationship to one another.

It is important to recognize that causality cannot be established definitively through epidemiologic studies; however, such studies are a powerful tool that can provide important evidence to suggest causality, as well as information regarding the strength of an association between diseases.\(^1\)

To evaluate the causal significance of observed associations, Hill proposed a number of well-known criteria,\(^1-3\) including the following:
- strength of association—the stronger the association determined in observational studies, the more likely it is to be causal;
- consistency (or replication) of findings among studies—a relationship is more likely to be causal if it is observed repeatedly in different subject populations using varying study designs;
- temporality—the exposure to a factor has to clearly precede disease onset for it to be causal (however, while this is the strongest of Hill’s criteria, the time of exposure relative to disease onset in retrospective studies can be difficult to determine);
- biologic gradient (or dose response)—there should be a relationship between the magnitude of the exposure and the frequency or severity of disease;
- biological plausibility—to establish a causal relationship, it is important to identify a scientifically valid mechanism by which the putative causative factor can produce the disease;
- experimental evidence—a randomized clinical trial (RCT) with appropriate controls provides stronger evidence than can be obtained from observational studies.

Although these are good guidelines, they are not foolproof. There are many examples of exposures that failed to meet the criteria and still were shown to be causal, as well as examples of exposures that met the criteria and proved not to be causal.

A number of study designs have been used to study the relationship between periodontal and systemic diseases. The majority of these have been epidemiologic studies that fall into two general categories: retrospective and prospective. Most retrospective studies are case-control studies, and most prospective studies are cohort studies. As noted above, epidemiologic studies can suggest causality and indicate strengths of associations. On the basis of findings of such studies, hypotheses can be generated that are tested in prospective clinical trials.

Some additional terms are used in discussing observational studies:
- Risk is the probability of a person’s developing a disease during a given period.\(^4\)
- Risk factors are variables associated with an increased risk (probability) of developing a disease. They may be a cause of the disease or they may be demographic, such as age or sex.
- Relative risk is the risk in an exposed group compared with that in the unexposed group. For example, if twice as many smokers as nonsmokers develop heart disease, the relative risk is two. Relative risk is a measure of the association between the exposure and outcome, but it does not indicate whether the association is causal. In a case-control study, the outcome measure is called the “odds ratio,” which is an estimate of the relative risk.

**Study designs.** Three main study designs have been used to study periodontal and systemic diseases: case-control studies, cohort studies and RCTs.

**Case-control study.** A case-control study is a retrospective study in which a group of subjects who have a given disease (cases) is compared with a control group of people who do not have the disease to determine if the group with the disease has been exposed to factors that the control group has not. These studies often depend on the accuracy of subjects’ recall of presumed disease-related factors. Case-control studies are the type of observational study conducted most commonly, as they are relatively short in duration and less expensive than cohort studies. However, they are susceptible to problems such as selection bias and recall bias that may lead to results less reliable.
than those of other study designs.

Cohort study. A cohort study is a prospective study in which groups of subjects (cohorts) are selected on the basis of their exposure to presumed causative factors and followed forward in time to see how many members of each group get the disease. This is expensive and time-consuming, especially when the study involves chronic diseases with long induction periods. However, this study design provides more accurate data regarding exposures and outcomes than does a case-control study, because it eliminates recall bias and control selection and minimizes selection bias. Case-control studies usually are conducted initially to study potential causative factors, with cohort studies conducted subsequently if evidence of a disease association is found.

Randomized controlled trials. RCTs are used to test therapeutic and preventive measures and can provide presumptive evidence of disease causation. They usually are conducted after observational studies provide strong evidence of associations that will justify their cost. They can provide much stronger evidence than can observational studies, because randomizing the study participants to treatment and control groups avoids many of the biases that can affect observational studies.

However, RCTs also have potential limitations, including subjects’ noncompliance with the protocol, loss of subjects to follow-up and loss of blinding. In addition, the cost and time involved in conducting an RCT for a chronic disease such as heart disease might make it impractical.

CHALLENGES IN INTERPRETING STUDY RESULTS

As noted above, the results of observational studies—and particularly case-control studies—can be distorted by many factors. These factors include biases, misclassification and measurement error, confounding, and effect modification (also called “interaction”).

Bias. A bias is “any systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure’s effect on the risk of disease.” In 1979, Sackett identified 24 biases. Many more have now been identified. Following is a list of a few of the major biases.

- Selection bias: An error in the method of study participant selection that results in a relationship between the exposure and disease in the study population different from that relationship in the general population.
- Information bias: Errors in data collection that lead to misclassification.
- Recall bias: An information bias in which subjects with disease (cases) tend to recall past exposures better than controls.
- Nonrespondent bias: People who agree to participate in a study differ from those who refuse to participate.
- Self-selection bias: People who volunteer to participate in a study differ from those who do not (they often are at higher risk).
- Publication bias: Journals are more likely to publish studies with significant results than those with negative results. This means that a review of the literature might not provide a balanced view of research results.

Misclassification. Misclassification is an error caused by inaccuracy in measuring exposures or disease status. It can make the observed association appear either stronger or weaker than it actually is.

Confounding. Confounding is a mixing of the effect of an exposure with the effect of another variable that is associated with the exposure and is an independent risk factor for the disease. For example, consider a study that found an association between drinking alcoholic beverages and lung cancer. It is known that people who drink are more likely to smoke (the exposures are associated) and that smoking is a major risk factor for lung cancer (independent risk factor). If smoking is not considered in the data analysis, drinking alcoholic beverages will appear to be a strong risk factor when, in fact, alcohol is not a risk factor for lung cancer and the results were due to the smoking.

Effect modification. Effect modification occurs when the effect of the risk factor on an outcome can vary, depending on the value of another variable. Smoking has been identified as an effect modifier in the associations between periodontal disease and both coronary heart disease and chronic obstructive pulmonary disease.

For example, in one study, participants with severe periodontal disease who also were smokers...
had almost six times the risk of experiencing a heart attack as did participants without periodontal disease. Participants with severe periodontal disease who were not smokers had no increased risk of experiencing a heart attack.\textsuperscript{12} This illustrates the difficulty in understanding the true relationships between periodontal disease and systemic diseases. Such problems can be resolved if future studies assess confounding and effect modification by smoking and other variables.\textsuperscript{14,15}

**Example: challenges in study interpretation.** A simple example will illustrate some of the issues inherent in interpreting the results of observational studies.

Consider a hypothetical case-control study investigating the relationship between drinking caffeinated coffee at dinner and the risk of having automobile accidents in the evening. In this study, coffee drinkers were found to be twice as likely to have an accident as those who did not drink coffee, with the difference being statistically significant as determined by a $P$ value < .05. How do we interpret these results?

While in this hypothetical situation drinking caffeinated coffee could be the cause of increased automobile accidents, there are other possible explanations for these results. They could be due to chance (a significant $P$ value means only that the observed association is unlikely to be due to chance). Perhaps people were more likely to drink coffee if they felt tired, and fatigue is a risk factor for (or a cause of) the accidents (confounding). Perhaps a higher percentage of the coffee drinkers in our study were male compared with coffee drinkers in general, and males are known to have a higher accident rate to start with (selection bias, confounding). Caffeine might have a greater effect on people when they drive if they also smoke (effect modification).

There also could have been mistakes in how the exposure and outcomes were measured. Some people might not have remembered correctly if they drank coffee that night (information bias). The memory of those who were in accidents might be worse because of the stress (recall bias). Some study participants might have told us what they thought we wanted to hear (information bias). Coffee drinkers might have been less likely to participate in the study if they had had an accident (nonresponse bias). There also could have been errors in our data management. For example, mistakes might have occurred during computer data entry, such as an accidental reversing of the codes for “drinker” and “non-drinker” (misclassification).

This example demonstrates problems inherent in the study design that could seriously distort results, and it points to the need for care in the design, conduct and analysis of observational studies.

**CONCLUSIONS THAT CAN BE DRAWN FROM EXISTING DATA**

The Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group\textsuperscript{16} (reporting in The British Medical Journal) and Shekelle and colleagues\textsuperscript{17} are among those who have developed formulas to help assess the strength of scientific evidence. So far, data regarding the association between periodontal and systemic diseases have come primarily from observational studies, which, as we have noted, are fairly low on the scale for determining causality. While there is some evidence of an association between periodontal disease and a number of systemic diseases, the evidence is not yet strong enough to justify a conclusion that periodontal disease is a cause of these diseases.

**FUTURE STUDIES TO STRENGTHEN THE DATA**

Observational studies provide us with valuable estimates of the relationship between periodontal and systemic diseases in the form of measures of association.\textsuperscript{18} These are just estimates, however, since nearly every such study has the types of errors that we have discussed.\textsuperscript{19} If future observational studies can overcome some or all of these errors,\textsuperscript{15} the accumulation of studies that have different designs, populations and combinations of biases will lead to a better understanding of periodontal/systemic disease relationships.\textsuperscript{6} In addition, if future well-designed RCTs are able to demonstrate consistently that preventing or successfully treating periodontal disease reduces the risk of systemic diseases, they will provide strong evidence that periodontal disease is one of the causes of, or significant risk factors for, systemic diseases. The accumulated evidence from properly conducted studies will enable us to arrive at a good understanding of the true interrelationships between these diseases.

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