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Causal theory and the etiology of periodontal diseases

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A clear understanding of the best means by which to prevent and treat periodontitis requires a clear understanding of its cause(s). The purpose of this paper is to critically review the general principles of disease causation and causal theory, and to introduce accompanying models of causality that elucidate principles of causation, confounding and effect measure modification (interaction) for application to epidemiological studies of periodontitis. The aim of this review is to focus on the multi-causal nature of periodontal disease, and the importance of specifying the causal assumptions informing the design and analysis of epidemiological studies of periodontal disease through development and inclusion of causal models. In order to assist the discussion, we present working definitions of key terminology in Table 1.

It is not our purpose to contend that bacteria are not causal agents of periodontal disease, as has been argued by some. Instead, we focus attention on the causal roles of 'other agents' as supported by causal theory. Examples of such 'other agents' may include factors such as tobacco smoking, hyperglycemia, occlusal trauma, a 'hyper-inflammatory' trait, and/or an ineffective immune response, for example due to failure to produce the enzyme cathepsin C in Papillon–Lefèvre syndrome (22). Each of these factors appears to contribute to irreversible periodontal attachment loss in some patients, but not necessarily in others. In addition, our discussion of a model of pathogenesis that focuses on primary causation by bacteria is used by us in this review as a means to highlight the importance of causal models in periodontal epidemiological research, particularly in the assessment of confounding.

Causation and the need for causal models

Defining the general notion of causation has been an iterative process over several centuries. Current views on causation have been profoundly influenced by early philosophers in the field, such as David Hume, John Stuart Mill and Bertrand Russell, who emphasized the importance of the temporality of events and identification of alternative explanations for observations other than cause and effect (i.e. confounding) (27). More recent contributions include the advent of the randomized trial (54), the development of causal criteria (23) and discussions of statistical inference (9). Enduring over the centuries has been the notion of the counterfactual ideal for identification of causes (14, 15, 33), in which a factor is determined to be causal if, under identical repetitions in the same space and time continuum, its presence results in the outcome under study and its absence prevents the outcome. For example, smoking would be considered a causal factor in a smoker with periodontitis, if this patient, counter to fact (and all else being equal) had not smoked and not developed periodontitis. Susser (57) broadly summarized this concept by defining a cause as 'something that makes a difference'. Others have provided more explicit and counterfactually based definitions of causation that facilitate more extensive application in epidemiology. For example, Rothman et al. (52) contend that a cause is 'An event, condition, or characteristic that preceded the disease onset and that, had the event, condition, or characteristic been different in a specified way, the disease either would not have occurred at all or would not have occurred until some later time'. Although Susser's definition may be more appealing conceptually, Rubin's (54) work in the 1970s with randomized experiments has promoted acceptance of Rothman's more detailed explanation of causation under the counterfactual ideal.

Simple application of the aforementioned concepts of causation as outlined by Rothman should reveal that disease outcomes likely result from multiple causes. However, the natural human tendency towards causal thinking results in perseverance in

attempts to identify the singular cause of an observed event. This innate emphasis on single causation is often manifested in formal investigation of disease outcomes. In order to avoid this natural misconception and to acknowledge the complexity of multifactorial disease causation, conceptual or theoretical models of causation have been developed, and have proven to be useful in discussions of causation (3, 27, 57). Furthermore, understanding that causes of disease rarely act in isolation, causal models assist in distinguishing between those factors that truly affect disease frequency (e.g. risk factors) and those factors that result in spurious observed associations (e.g. confounders) (46).

Several models of causation have been deployed, vetted and utilized as functional illustrations of the counterfactual ideal and accepted notions of causation (12). Three have achieved widespread acceptance: the potential outcomes model, the sufficient-component cause (SCC) model, and directed acyclic graphs (DAGs). A general overview of the potential outcomes, SCC and DAG models is provided. A more thorough explanation and accompanying illustrations are provided for the SCC and DAG models in order to highlight their greater applicability in scientific investigations, whereas the potential outcomes model is only introduced to aid in thoughtful application. The SCC model is most useful in describing disease causation by multiple causes and their interactions, while the DAG model is well suited to investigating sources of confounding and planning the design and analysis of clinical epidemiological studies accordingly.

Table 1. Definitions of terminology used in this review

Term	Definition
Cause	An event, condition or characteristic that preceded the disease event and without which the disease either would not have occurred at all or would not have occurred until some later time (52)
Causation	May be used interchangeably with the term 'etiology' to refer to the constellation of causes that produce disease
Confounding factors	Covariates that are not on the causal pathway, cause or affect disease occurrence in the reference population, and are not balanced in the index and reference populations, thereby producing confounding (15)
Confounding	The situation in which the crude (uncontrolled) measure of effect differs from the measure of effect adjusted (controlled) for a potential confounder (collapsibility-based definition) (16)
Effect measure modification	A common situation in which an effect measure changes over values of some other variable (51)

Potential outcomes model

In concert with the counterfactual ideal, the potential outcomes model was orginally developed by Neyman within the context of randomization (39). It was later extended beyond randomised experiments by Rubin (55). It models the statistical probabilities of outcomes other than the factual outcomes (i.e. 'potential outcomes') (32). The potential outcomes model was the first model to formalize the notions of cause and effect that were prominent in philosophy at the time (12). According to the model, potential outcomes must be independent (e.g. non-contagious), and the calculated probabilities rely on the assumptions that each individual in the population could have received any of the exposures under study, and that non-zero probabilities exist for each individual's potential outcomes, regardless of their factual outcomes. Both *individual*-level and *population*-level effects of exposure can be calculated using this model.

The model requires a possible counterfactual exposure condition as well as associated potential outcome probabilities. As a result, the role of bacteria in the development of periodontitis cannot be considered as a candidate for causation due to lack of a possible counterfactual condition. Instead, the model implies that the role of bacteria is one of necessity. This notion concurs with our current understanding that disease simply does not occur without the presence of bacteria. This same logic can be applied to other necessary states such as the presence of a tooth, for example. Without a tooth, the risk for (or potential outcome of) disease does not exist (i.e. a zero-probability outcome). The potential outcomes model forces recognition that all evaluations of predictors of periodontal disease must be performed under a paradigm in which bacteria, and other factors necessary

for disease outcomes to exist, are present. By extension, it is unreasonable to control for these necessary factors in evaluation of other predictors of disease outcomes, as this would violate the model.

Although it is only possible to implement the potential outcomes model through computer simulations, the model emphasizes the importance of a reference or comparison group that is representative of the disease experience the exposed group would have had if they had not been subject to the exposure under investigation (counter to the fact). In the previous example, this necessitates the non-consideration of bacteria in evaluation of other factors. The most notable epidemiological designs that achieve this standard are randomized trials and case-crossover studies (12). Both designs inherently increase the likelihood that the unexposed experience can stand in for the 'counterfactual' exposed experience. In addition to illustrating the importance of a well-defined reference group, the potential outcomes model enables theory-anchored interpretation of measures of effect and provides an understanding of threats to the validity of those measures (e.g. confounding) that can be applied both thoughtfully and practically to epidemiological research (34).

Sufficient-component cause model

The sufficient-component cause (SCC) model was introduced by Rothman in 1976 in an attempt to facilitate communication about causes of disease (49, 50). Since then, it has received widespread attention in the epidemiological literature, including further adaptations of the model beyond its original intent (24, 25, 45, 59, 61). The SCC model, which is also referred to as 'causal pies', is another representation of the counterfactual approach and multi-factorial causation. Under the SCC model, no single factor produces disease in isolation. Instead, disease is considered to be the result of multiple causes acting in concert, removal of any one of which would result in the disease either not occurring by that mechanism or not occurring until a later time. In Rothman's SCC model, individual causal factors are represented by individual slices of a whole 'pie', and a completed pie is representative of a unique, wholistic causal mechanism that is sufficient to produce disease in an individual (Fig. 1). In accordance with multi-factorial disease etiology, the occurrence of disease in a population is represented by a number of different completed pies with unique combinations of causal components (Fig. 1). Analogously, while no individual disease outcome has a single cause, disease outcomes across a large population can rarely be attributed to a single causal mechanism, i.e. a unique combination of causal factors that causes disease in all individuals in a population.

To relate casual pies to the potential outcomes model already described, causal mechanisms rather than individuals are the basic units of analysis used to determine potential outcomes in individuals (12). Furthermore, the potential outcomes model is limited by its inability to address the actual mechanisms producing the presence or absence of disease as well as those producing non-additivity of disease risk (e.g. synergism) (11). This additional ability of the SCC model allows consideration of synergistic causes, and thus the model may have more practical applications than the potential outcomes model (7).

Component causes

Each etiological factor contributing to a disease outcome is represented graphically by a portion of a circle – more appealingly described as a slice of a pie. Rothman refers to each of these as 'component causes' of disease. Component causes of disease are synonymous with the terminology 'risk factor'. In theory, each component cause must have a specified referent condition, although this is not explicitly shown here. Among these causal components of disease is a component set aside for unknown causes, i.e. those

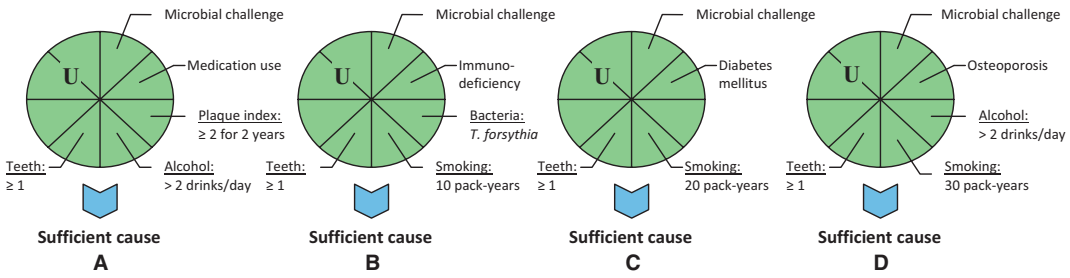

Fig. 1. Hypothetical classes of sufficient causes for periodontitis.

unmeasured co-factors that are present regardless of the individual's exposure or disease status. These are represented by the slice labeled 'U' (Fig. 1).

Following the counterfactual definition of causation, if a component cause for a single disease mechanism were to be blocked, disease would not occur by that mechanism; this does not of course preclude the possibility that the same clinical disease entity may result from a different mechanism(s). Causal components are most often the focus of etiological/epidemiological research. Examples of component causes of periodontal disease are shown in Fig. 1.

Sufficient causes

Once an individual has accumulated a set of component causes that complete a given disease mechanism, that constellation of component causes is deemed sufficient to produce disease, and their aggregate state is termed a 'sufficient cause', represented by an entire circle or pie. According to the counterfactual definition, sufficient causes should be restricted to the combination of component causes that is minimally sufficient to produce disease, such that blocking the action of just one component cause in a sufficient cause would render that sufficient cause incomplete, preventing onset of disease by that mechanism. For example, if 25% of periodontitis cases in a population were the result of sufficient causes in which diabetes was a component cause, complete prevention of diabetes in the population could result in a maximum 25% decrease in the incidence of periodontitis (24, 25).

It is important to note that, in accordance with the above definition, the components of each pie (the component causes) are those factors that contributed to causation of disease in an individual, and not all factors present in that individual. For example, smoking is absent from sufficient cause A in Fig. 1, but this causal mechanism may act in a smoker, i.e. smoking may not have been part of the causal mechanism in a smoker with periodontitis. In other words, assuming that the patient with sufficient cause A was a smoker, she would have developed periodontitis at the same time even if she had not been a smoker, all else being equal, i.e. preventing smoking would not result in prevention of disease occurrence, hence its absence from the causal pie.

Under the SCC model, the absolute effect of the index condition, compared to the reference condition, is the number of sufficient causes (disease) among those with the index condition (total exposed) minus the number of sufficient causes (disease) among those with the reference condition (total unexposed). Synergy, or biological interaction, between component causes arises when one or more sufficient causes contain two purportedly synergistic component causes, and the resultant disease risk due to that mechanism is greater than the summed risks across causal mechanisms containing each component individually and mechanisms containing neither component.

Necessary causes

Component causes that appear in every causal pie sufficient to produce disease are termed 'necessary' causes. For example, it is understood that periodontal disease is a result of an inflammatory response to the presence of bacteria in the gingivae. If this is true, periodontal disease would not occur in the absence of bacterial pathogens. Therefore, the presence of these periodontal pathogens would be considered a necessary cause of periodontal disease and thus would be represented in every sufficient cause of disease. Given the counterfactual definition which supports multi-factorial etiologies, no component cause, although perhaps necessary, is sufficient by itself to produce disease. Therefore, the presence of bacterial pathogens alone cannot be responsible for disease occurrence. In Fig. 1, it is apparent that the presence of a microbial challenge is a necessary cause of periodontitis, as it acts in each of the sufficient causal mechanisms. Thus, the conclusions drawn using the SCC model with regard to bacteria as a cause of periodontitis are akin to those drawn using the potential outcomes model.

Implications of the SCC model and applications in periodontitis

The SCC framework provides assistance in understanding the multi-factorial causation of periodontitis. Primarily, the SCC model removes the emphasis on single-agent causation through the visual depiction that no single cause is sufficient to produce disease. When this model is specified, it makes clear the fallacy of seeking to identify *the* cause of periodontitis. Specifically, it serves no purpose to talk about bacteria as *the* cause of periodontitis, under the recognition that other causal factors must be in play in order to produce disease. Furthermore, although bacteria are a necessary cause of periodontitis, the model makes it clear that other components do not simply modify the disease risk but instead

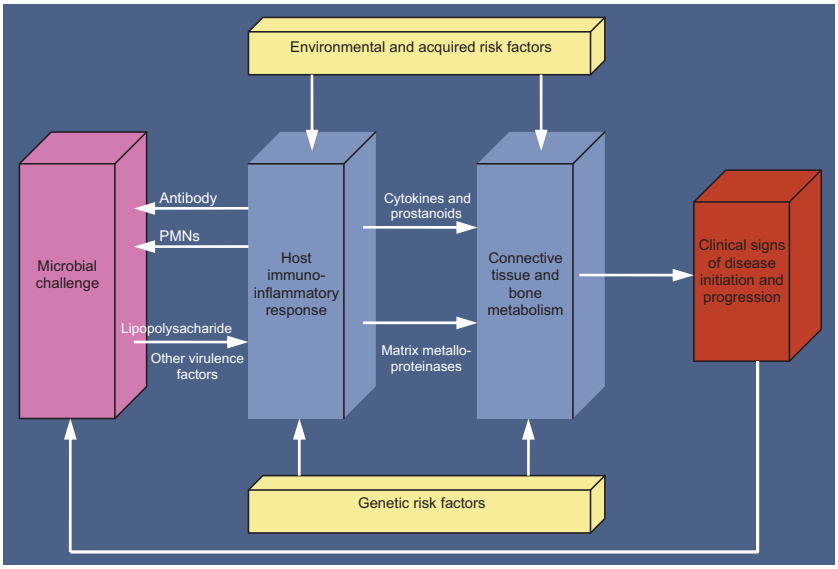

Fig. 2. Page & Kornman (42) model for the pathogenesis of human periodontitis. PMNs, polymorphonuclear leukocytes.

each play a causal role in disease development. Even further, component causes differ in number and magnitude of impact from one patient to the next, explaining the wide heterogeneity of the periodontitis phenotype. Thus, causal mechanisms of inflammatory periodontitis differ between patients, as has been recognized for some time (42).

The model proposed by Page & Kornman (42) in 1997 is currently perhaps the most popular model of the pathogenesis of periodontitis (Fig. 2). The model and its graphical presentation has probably contributed to the notion of bacterial plaque as the primary cause of periodontitis, partially due to the microbial challenge featuring prominently in terms of color and position, and partially due to it being misinterpreted as an etiological model rather than a model of pathogenesis. The model is reasonable in suggesting that microbial challenge triggers an inflammatory response, leading to connective tissue damage and ultimately periodontitis in susceptible patients. However, when considering disease causation, this order of events does not give priority to any of the component causes, and certainly does not mean that factors that affect the host response or processes associated with connective tissue destruction are 'secondary' factors. This should be self-evident given that blockage of any component cause would prevent disease. This has important implications, as all component causes are, at least theoretically, a potential therapeutic target. Intervention on all component causes could be considered and, if available and feasible, such interventions should be evaluated in terms of their effectiveness and their risk/benefit and cost/benefit ratios. It is important to note that successful intervention on a single component cause will block disease occurrence. Hence, at a population level, a reduction in cigarette smoking alone will, all else being equal, result in a lower incidence of periodontitis. Alternative models have been proposed that abandon the linear depiction of a bacterial challenge leading to periodontal breakdown and recognize the complex interplay of multiple causal factors in the pathogenesis of disease (Fig. 3) (6, 41).

The SCC model also facilitates the identification of necessary causes, such as the mere presence of bacteria, that are not appropriate for consideration in studies of other causal components. When a true necessary cause exists, it is not meaningful to evaluate or even to measure it in studies of other components of causal mechanisms. For example, when evaluating the effect of smoking behavior on the occurrence of periodontitis, consideration of the presence or absence of periodontal pathogens is rendered unnecessary by virtue of the fact that bacteria must be present in all causal mechanisms of disease. In the case of periodontitis, this should be particularly obvious as

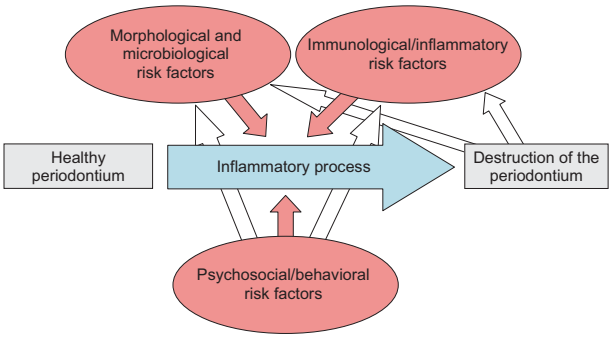

Fig. 3. (Adapted from Dörfer (6) with permission.) Alternative illustration of the interplay of multiple causal factors in the pathogenesis of periodontitis.

the oral microflora is omnipresent. Thus, the SCC model also illustrates the need for more specific hypotheses with regard to the microbial causes of periodontitis, either in terms of specific microbiota or microbial complexes (Fig. 1, sufficient cause B) or in terms of their quantity (Fig. 1, sufficient cause A), which in turn allows for consideration of appropriate therapeutic interventions.

In addition to providing an illustration of the counterfactual notion of causality, the SCC model lends meaning to the concepts of exposure interactions; particularly biological interactions or synergies, evaluated on the difference (or absolute) scale (11, 25, 58, 61). For example, confirmation of the hypothesis that smoking and alcohol, operating in concert, were synergistic in their effect on development of periodontitis would necessitate a greater risk for disease arising through a sufficient cause which contained both component causes (Fig. 1, sufficient cause D), than the total disease risk arising from sufficient causes containing each component individually and those containing neither. Understanding and specifying the biological model of periodontal disease in this sense is important to discussions of biological interaction between causal components (3). It is important to note that the implications of interactions between causal components in the SCC model usually pertain only to biological interactions evaluated on the difference scale. They do not typically inform statistical interaction in regression models, which are scale-dependent and not always reflective of biological interaction (11, 53, 58). Discussion of statistical interaction on the relative vs. additive scales is beyond the scope of this review, and interested readers are referred to Rothman for a gentle treatise (51). The SCC model similarly allows evaluation of dose-dependent effects, such as smoking intensity or duration (Fig. 1, sufficient causes B, C and D).

Finally, the SCC model provides a foundation for the terminology used in epidemiological evaluations. Each component within a sufficient causal mechanism plays a causal role in the development of disease, such that accumulation of additional component causes places an individual much closer to the onset of disease. Therefore, a component cause can be referred to as a 'risk factor' for disease. Under the SCC model, there is no basis for use of the term 'modifiers' to describe component causes. The term 'modifier' is more appropriately reserved for variables responsible for effect measure modification (Table 1). Modification on the difference scale is observable in the model through causal co-action of components as previously described (smoking and alcohol) (61). Under the SCC framework, it is clear that causal components such as diabetes mellitus that do not experience co-action with other components do not modify disease progression but instead play a causal role in its initiation.

Causal directed acyclic graphs

Causal directed acyclic graphs are graphical depictions of statistical associations between causal components and the disease outcome of interest at a population level. Causal graphs (or causal diagrams) have been used for a long time to evaluate causal associations and to analyze non-experimental observations under both simplistic [e.g. webs of causation (31)] and more complex [e.g. structural equation modeling (43, 44) and path analysis (8)] paradigms. However, use of causal graph theory as illustrated by directed acyclic graphs (DAGs) has recently gained momentum in the epidemiology literature, as indicated by its popularity in the methodological literature as well as its increasingly common inclusion in papers describing etiological research. Like the causal pie theory, causal graph theory requires investigators to expound their assumptions of the underlying causal model linking exposure to disease. Unlike causal pies, however, causal graphs provide the ability to test the validity of approaches used for evaluating a causal mechanism by application of a rule-based, visual evaluation of charted causal relationships that have mathematical underpinnings in the counterfactual ideal. However, unlike the potential outcomes and SCC models, there is no inherent technique to quantify associations, i.e. estimate effects based on information in the graphs. Thorough explanations of DAG theory, its terminology and applications are available elsewhere (13, 43), including explanations geared specifically to a dental research context (35).

Directed acyclic graphs basics

A causal DAG is constructed by specifying directional paths between causal components and the disease outcome. Each directed path is representative of the statistical association that is present between the two components as well as the hypothesized causal relationship. The resultant directed graph is termed 'acyclic', in that it is not permissible for directed pathways to exist that begin with the causal component of interest (i.e. the primary exposure), progress to the disease outcome, and then return to the

exposure in a cyclic manner. The primary aim of etiological research is to eliminate all 'nuisance' pathways from exposure to disease other than that of causal interest (Fig. 4A). The most basic causal DAG is the common illustration of the principle of confounding: two directed paths originating out of a third variable that represent its causal role in both the exposure and the disease (Fig. 4B). Without control of this third variable, an open or 'back door' path exists from exposure to disease through this third variable. In order to block the path from exposure to disease through a confounder, we place a box around the variable to signify its control (Fig. 4C). By doing so, the only available path from exposure to disease is that of direct causation (Fig. 4A). The basic graph in Fig. 4C illustrates the three characteristics of a variable that are necessary to qualify it as a potential confounder: (i) causally associated with the exposure (arrow from C to E), (ii) independent predictor of disease (arrow from C to D), and (iii) not a causal intermediate, i.e. not on the causal pathway from exposure to disease (14, 37).

Although control of a variable will block some paths, it may also open paths by inducing a new statistical relationship as a result of its control. This is possible when the variable being controlled is what is referred to as a 'collider'. A collider is a variable that is a result of two causal components that are independent of one another ('C' in Fig. 4D). A 'back door' pathway from exposure to disease cannot pass through a collider. However, by controlling for this variable, the two independent predictors become marginally associated with one another (e.g. conditionally dependent). If they also have associations with exposure and disease, control of their common effect (C) will open a back door pathway from exposure to disease (Fig. 4E). This special situation is referred to as 'M' bias (10), due to the shape of the causal relationships. As a causal DAG becomes more complex, these two basic understandings of DAG theory assist in identifying a minimally sufficient set of variables for analytical control. DAGs also provide assistance in identifying those variables where control is inappropriate or unnecessary. For example, if a collider is also a confounder, control of that confounder would also necessitate control of one of the variables associated with it in order to block the path from exposure to disease other than that of direct causation, but not both variables (Fig. 4F). Additionally, if variables are only associated with exposure or disease and are otherwise not part of the causal structure, their control will decrease statistical efficiency.

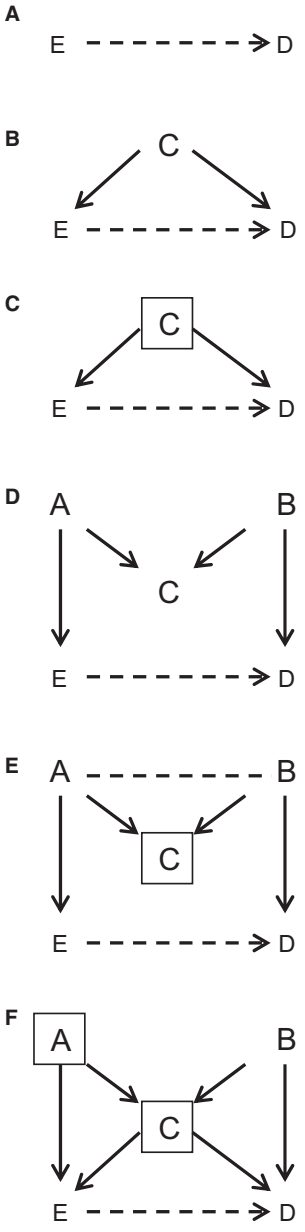

Fig. 4. Causal paths among hypothetical variables. E, explanatory variable; D, dependent variable. (A) Basic causal path from E to D. (B) Basic confounding of E–D association by hypothetical variable, 'C'; indicates an open alternative path through E–C–D. (C) Control of confounding by C in E–D association; alternative path through C is blocked. (D) Depiction of 'M' bias due to causal structure among hypothetical variables; open alternative path through E–A–C–B–D. (E) Induced statistical association between hypothetical variables A and B by control of C; open alternative path through E–A–B–D. (F) Depiction of minimally sufficient covariate control by hypothetical variables A and C; all alternative paths blocked.

The depiction of effect measure modification within a causal DAG has recently been developed, but requires more understanding of DAG theory than is

presented here (60). Causal DAG theory has also successfully depicted mechanisms of selection bias (20), and an introductory depiction of measurement bias (19, 21), both of which are beyond the scope of this review but represent useful applications for etiological research.

Indications for use of DAGs and applications in periodontal research

Directed acyclic graphs primarily illustrate dependencies between variables that have implications for the validity of estimated measures of effect (e.g. confounding). Use of DAGs in both the design and analysis of epidemiological studies forces consideration of confounding by multiple factors, and also the possibility for inducing bias through inappropriate control of other factors. The latter point is of particular importance given that even classic stratification on demographic variables may induce more confounding than it actually controls in evaluation of some exposure–disease associations. When there is little to no confounding in an observed association, conservative control of one factor but not others has the potential to increase confounding.

Analyses in epidemiological research of the etiology of periodontitis are frequently overburdened by control of factors that are only associated with periodontitis and not at all with the determinant under study (e.g. non-confounders). This approach may decrease the statistical efficiency, and worse, may induce additional confounding or mask possible effect measure modification. Focus on the control of factors that are only associated with development of periodontitis, particularly those that are most 'proximal', is evidence of singular focus on the *biological* model of periodontitis in epidemiological research instead of the *causal* model for the exposure–disease association under study. For example, a recent review evaluating the role of alcohol use in development of periodontitis criticized studies that excluded analytical control of dental plaque or proxy measurements of dental plaque given its known etiological role in the development of periodontitis (1). If a factor is purely a predictor of the outcome, it is unlikely that there is an imbalance of that factor across the exposure of interest, and therefore no possibility for confounding by that factor in a simplistic model. However, its control may result in an imbalance across strata of another variable that becomes associated with both exposure and disease via such control (see Fig. 5). In a causal model evaluating the effect of alcohol consumption on development of periodontitis, dental plaque is not causally associated with alcohol use, and, at most, would probably be on the causal pathway from alcohol use to development of periodontitis. Control of dental plaque analytically should be considered inappropriate unless it is deemed necessary in order to block paths from exposure to disease that were opened through control of other variables.

It is possible that investigators may actively choose to control for causal intermediates in an attempt to identify the specific causal pathway from exposure to disease and thereby estimate the exposure's direct effect. The ability to do so in an unbiased manner is dependent upon strong assumptions that are difficult to meet in practice but can be evaluated through use of DAGs (4). When these assumptions are not met, control of a causal intermediate will most often result in a biased estimate of the effect of the exposure – how much bias and in what direction is dependent upon the causal relationships surrounding that variable. The appropriateness of control of variables for measurement of direct and indirect effects can also be evaluated using the potential outcomes model (47).

Interestingly, criticisms of epidemiological research evaluating the role of periodontal disease in development of other systemic conditions suggest that the role of confounding in many of the associations has been overlooked (26, 63). The use of DAGs becomes much more critical when considering oral–systemic disease associations, as the causal structure becomes more complex and is more likely to contain common causes (e.g. confounders). Furthermore, longitudinal studies with repeated observations, in particular, are likely to suffer from time-dependent confounding, and also provide the additional opportunity for a covariate to play a dual role as a

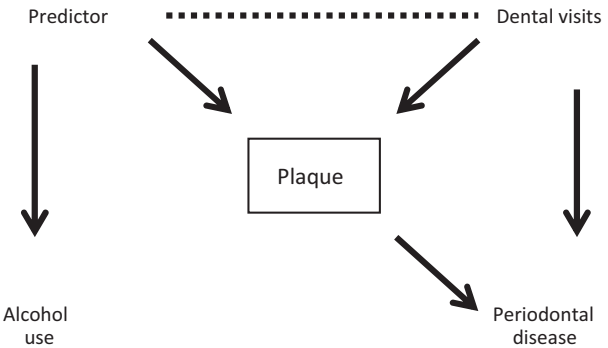

Fig. 5. Hypothetical causal structure for evaluations of the causal effect of alcohol use on periodontal disease.

confounder and a causal intermediate over time. Blanket control of these covariates with dual roles would be inappropriate for the reasons described above. Use of DAGs highlights this issue, and may suggest the use of analytic techniques, such as marginal structural modeling, that are capable of addressing the confounding effects only (18, 48).

Lastly, specifying a causal DAG for the association under study visually encourages, at a minimum, the consideration of effect measure modification, and, ideally, analytical evaluation of effect measure modification through stratified analyses to verify causal assumptions when possible.

Discussion

The etiology of periodontal disease and its associated sequelae has received widespread attention in epidemiological studies. It is clear that initiation of periodontitis and its progression are multi-factorial in nature, and that its potential role in the development of subsequent systemic diseases is only one of several causal factors contributing to such complex diseases (28, 30, 62). However, discussions of epidemiological studies on the causation and progression of periodontitis are littered with inconsistencies regarding the specific causal pathways, possible modifiers, and important confounding factors. Although many periodontologists agree that host factors such as diabetes mellitus, or external factors such as smoking behaviors, play a role in the development of periodontitis, some reviews contend that bacteria are the primary etiological agent in disease development, and that host factors such as diabetes only modify the disease process or affect the disease severity and/or extent. In addition to such discussions of disease causation, commentaries regarding the appropriate evaluation and control of confounding factors in epidemiological studies of periodontitis are similarly inconsistent (17, 29, 30, 36, 38, 40, 42, 56).

These inconsistencies within the literature probably arise as a result of some investigators focusing primarily on the *biological* model of disease (such as the Page & Kornman model, in which periodontitis is proposed to be initiated by bacterial colonization of the dento-gingival complex and to progress linearly via immune and inflammatory processes) instead of focusing on the *causal* model for the particular exposure–disease association under epidemiological investigation (which involves evaluation within a specific exposure–disease framework in which the mere presence of the bacteria is frequently inconsequential). While both types of models are important when studying disease etiology, focus on the former (biological model) usually results in emphasis of single-factor causation by bacteria, with other factors exerting only a modifying influence. When this emphasis influences the epidemiological study of other causal factors, it results not only in inconsistent application of terminology, but even more importantly, inappropriate design and analysis of studies. Furthermore, it may hinder appreciation of the full range of potential therapeutic and preventative approaches available to addressing periodontitis. Lastly, movement away from a singular focus on a biological model in epidemiological investigations is necessary to understand disease at both individual and population levels (2, 5).

Conclusions

We are not the first to recommend that causal models be employed in the design and conduct of epidemiological research (2, 3, 5). Explicating causal assumptions in reports of epidemiological research is necessary to advance our knowledge of the true effect of different exposures on periodontitis, both for individual patients and also across populations, while also avoiding repetition of common mistakes. It serves no purpose to focus solely on the biological model of disease in epidemiological research other than to support causal assumptions associated with the exposure–disease association under study. Discussions of the etiology of periodontitis that propose *initiation* by bacteria and mere *modification* by host factors such as diabetes should have no place in epidemiological studies. Component causes are likely to be multiple in complex diseases such as periodontitis, and their quantum of effect and interactions in different individuals form part of the complexity of human biology and the phenotypic heterogeneity of complex diseases.

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