J Clin Periodontol 2006; 33: 104–108 doi: 10.1111/j.1600-051X.2005.00886.x

Journal of Clinical Periodontology

Confounding and effect modification: possible explanation for variation in the results on the association between oral and systemic diseases

P. V. Ylöstalo[1] and M. L. Knuuttila[2]

[1]Department of Periodontology and Geriatric Dentistry, Institute of Dentistry, University of Oulu, Oulu, Finland; [2]Oral and Maxillofacial Department, Oulu University Hospital, Oulu, Finland

Ylöstalo PV, Knuuttila ML. Confounding and effect modification: possible explanation for variation in the results on the association between oral and systemic diseases. J Clin Periodontol 2006; 33: 104–108. doi: 10.1111/j.1600-051X.2005.00864.x.

Abstract

Objectives: There is large variation in the results of studies on the association between periodontitis and systemic diseases. The variation might be explained by the fact that the association between periodontitis and systemic diseases is confounded, or the association might be modified by extraneous factors. In this article, we show, using simple examples, how confounding and effect modification may cause variation in results. In addition, these examples show that uncontrolled or partially controlled confounders can induce spurious associations.

Conclusion: Confounding and effect modification may explain the variation in the results of studies on the association between periodontitis and systemic diseases.

Key words: cardiovascular diseases; confounding; effect modification; oral diseases

Accepted for publication 8 August 2005

Although confounding and effect modification are basic concepts in quantitative research, they are not always treated in an appropriate manner in epidemiological studies on the association between periodontal and systemic diseases. In many reports, no stratification to detect possible effect modification or confounding and subsequent reporting of estimates is performed even when there is previous evidence that effect modification or confounding can exist.

The prevailing praxis to analyse the association between periodontitis and cardiovascular diseases (CVD) appears to be to use multivariate models such as a logistic regression model, for example, where potential confounders such as smoking and other risk factors for CVD are included in the model. An aspect that has often been ignored is that multivariate models with a single estimate require homogeneity of the effect across the different levels of the extraneous variables. This means, for instance, that the effect of exposure on outcome should be approximately the same among non-smokers and smokers, or across the different age groups. However, previous studies have shown that the strength of the association between periodontal diseases and CVD is different between smokers and never-smokers (Hujoel et al. 2002, Hyman et al. 2002).

The fact that the strength of the association varies may be because of effect modification or confounding, or both. Hyman et al. (2002) suggested that smoking modifies the effect of periodontal diseases on CVD by being a necessary cofactor. Several researchers have suggested that there is substantial confounding related to the measurements and operationalization of smoking history (Miettinen 1985, pp. 42–43, Scott et al. 2001, Hujoel et al. 2002, Spiekerman et al. 2003). Furthermore, variation in results may be because of random variation or biases related to the detection and reporting of periodontal diseases and systemic diseases.

Below, definitions of confounding and effect modification as well as some related concepts are presented. We also present some aspects related to the identification and subsequent

handling of confounding and effect modification. We demonstrate confounding and effect modification using algebraic examples, and the effect of incomplete controlling of confounders using simulation data.

Definitions of Effect Modification and Confounding

The basic difference between effect modification and confounding is that effect modification is a property of the effect while confounding can be considered a confusion of the effects (Rothman & Greenland 1998, pp. 120, 254). The term confounding refers to a situation where the categories of the exposure variable are different in relation to extraneous determinants (Fig. 1). Confounder is defined as 'an extraneous determinant of the outcome parameter in terms of which there is lack of comparability of the effects and/or populations' (Miettinen 1985, pp. 12, 321–322). For example, gender, age, health behaviour and socioeconomic status are often associated with the outcome and unevenly distributed among exposed and unexposed subjects, causing confounding.

Effect modification is the inconstancy in the magnitude of the effect across levels of another subject characteristic, while an effect modifier is a subject characteristic on which the effect depends (Miettinen 1985, p. 332). Normally, there always exists some effect modification, and rarely is there any basis to expect that the effects are equal in different categories or strata (Rothman & Greenland, p. 51). In periodontology, one example of effect modification is that smokers experience less reduction in probing depth after non-surgical periodontal treatment compared with non-smokers (Labriola et al. 2005). Another example of effect modification is the association between cyclosporine medication and gingival overgrowth, where gingival overgrowth is modified by the presence of gingival inflammation (Pernu et al. 1992). A variation in the effect in different subgroups (effect modification) and a lack of comparability between exposed and unexposed subjects (confounding) can exist simultaneously.

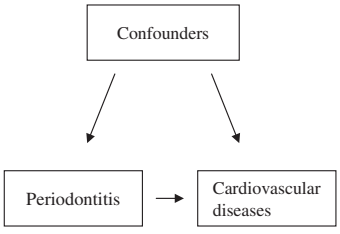

Fig. 1. Structure of confounding.

Interaction, which is the same as effect modification, occurs when the magnitude of the chosen measure of association between a variable and an outcome varies according to the level of the third variable. Rothman and Greenland make a distinction between statistical interaction and biological interaction. They define biological interaction as participation of two component causes in the same sufficient cause. This is sometimes also called causal coaction or joint action (Rothman & Greenland 1998, pp. 11–12). Statistical interaction refers to a situation where the interaction term (product term) has a statistically significant non-zero value in a regression model. In the case of a linear regression model, statistical interaction is a departure from additive relation, which corresponds to effect modification. Statistical interaction in the case of ratio measure (e.g. odds ratio, rate ratio) is a departure from a multiplicative relation. As many models are multiplicative in nature, biological interaction may be present without statistical interaction.

Evaluation of Effect Modification and Confounding

The decision concerning the treatment of effect modification is related to previous knowledge. There are alternatives relating to the study design on how to handle effect modification. Firstly, one can restrict the analysis to the homogeneous subdomain of the potential modifier. Secondly, one may study the relation with a design that assures the informativeness of the modification of the effect (Miettinen 1985, pp. 38–39).

Effect modification can be assessed using regression models or statistical tests such as a test of heterogeneity. However, Rothman and Greenland suggest the use of stratified data as an interim tool in data analysis. They suggest that in stratified data, stratum-specific estimates should be calculated first, and if effect modification is present, stratum-specific estimates should be reported since summary estimates do not convey information on the pattern of variation of stratum-specific estimates. In a situation where data are reasonably consistent, a singular estimate should be calculated either by summarizing stratum-specific estimates or by ignoring the stratification variable, depending on the situation, and the *p*-value for this should be calculated (Rothman & Greenland 1998, p. 254). As an alternative to stratification, regression models with product term can be used to obtain stratum-specific estimates. For the sake of simplicity, many researchers do not report stratum-specific estimates if the variation in the estimates is small.

The following criteria to identify actual confounders can be used: (1) it must be predictive for the disease, (2) it must be associated with the exposure under study, and (3) it must not be a link in the causal path between the exposure and the outcome. As the underlying causal models can be highly complex, the selection of confounders requires theoretical knowledge about their relation. Without theoretical knowledge, the causal model could be wrongly specified (Robins 2001, Merchant & Pitiphat 2002). It may be helpful to use a graphical representation of causal models, which may offer guidance in the selection of the relevant confounders to be controlled. There exist articles with examples of the use of causal graphs in epidemiological research, such as articles published by Robins (2001), Greenland & Brumback (2002) and Merchant & Pitiphat (2002). The latter gives examples on dental research and is highly recommended to all those who are engaged in quantitative research.

Confounding can also be evaluated and controlled in the analysis by using multivariate models, stratification or, in some cases, by standardization. A change in the magnitude of a parameter estimate in models with and without a potential confounder could be used to assess the magnitude of confounding. In the study design, confounding can be controlled by randomization (experimental studies), restriction or by matching either on an individual level or on a group level (observational studies). However, successful controlling of confounders depends on the quality of the measurement. In some instances, the measurement of confounders, such as age or gender, is quite simple, while in others it is not so straightforward. For example, the measurement of socioeconomic status or behavioural factors, such as smoking and drinking habits, can be more complex. The translation of such conceptual confounders into operational criteria may involve difficulties or

Table 1. Relation of smoking to periodontitis and to cardiovascular disease

Periodontitis				Cardiovascular Disease		
Smoking	yes	no		yes	no	
Yes	1000	1000	2000	450	1550	2000
No	200	1800	2000	150	1850	2000
	1200	2800	4000	600	3400	4000
RR = 5.00 (1000/2000)/(200/2000)				RR = 3.00 (450/2000)/(150/2000)		

failures, which may lead to the conclusion that a non-experimental study is not feasible (Miettinen 1985, p. 43).

Examples of Confounding and Effect Modification

Algebraic examples

In our first example, smokers have a fivefold risk of getting periodontitis, and a threefold risk of getting CVD compared with non-smokers (Table 1). In this example, those who have periodontitis have a 1.6-fold risk of developing CVD compared with those without periodontitis (Table 2).

In order to find out whether the relation is confounded by smoking, we calculated stratum-specific estimates for smokers and non-smokers. In this example, stratum-specific estimates showed that there was no association between periodontitis and CVD (Table 3). In this case, the association between periodontitis and CVD found in the unstratified data was because of confounding.

In the second example, those with periodontitis have a 1.6-fold risk of getting CVD compared with those without periodontitis. In this example, the relation between exposure and outcome disease was modified by a hypothetical susceptibility factor. The calculation of stratum-specific estimates showed that those with a susceptibility factor have a high risk for disease (RR = 4.3), while those without such a factor have a slightly elevated risk for disease (RR = 1.2). There was no confounding in this example as the susceptibility factor (modifier) was equally distributed among those who had periodontitis and those who did not (Table 4).

It is possible that the relation between exposure and outcome is simultaneously modified and confounded by an extraneous factor, as in our third example, where there were the same risks for CVD as shown in Table 2, but the stratum-specific estimates were different, being 1.5 and 1.0. As the susceptibility factor (modifier) was not equally distributed in the categories of the exposure variable (periodontitis), the modifying variable was simultaneously a confounder (Table 5).

Table 2. Relation of periodontitis to cardiovascular disease

Cardiovascular Disease			
Periodontitis	Yes	No	
Yes	240	960	1200
No	360	2440	2800
	600	3400	4000
RR = 1.56 (240/1200)/(360/2800)			

Example of confounding in the simulation data

We constructed a data set through simulation consisting of 1000 samples of 10,000 study subjects. This example illustrates the effect of confounding in a situation that resembles a normal epidemiological study with independent risk factors for both periodontitis and CVD and, in addition, more than one confounder. In this example, we demonstrate a situation where one of the confounders is left uncontrolled.

We constructed the data set so as to have no causal association between periodontitis and CVD. Both perio-

Table 3. Relation of periodontitis to cardiovascular disease according to smoking habits

Cardiovascular disease						
non-smokers				smokers		
Periodontitis	yes	no		yes	no	
Yes	15	185	200	225	775	1000
No	135	1665	1800	225	775	1000
	150	1850	2000	450	1550	2000
RR = 1.00(15/200)/(135/1800)				RR = 1.00(225/1000)/(225/1000)		

Table 4. Relation of periodontitis to cardiovascular disease according to a hypothetical susceptibility factor

Cardiovascular Disease						
No susceptibility factor				Susceptibility factor		
Periodontitis	yes	no		yes	no	
Yes	162	798	960	78	162	240
No	318	1922	2240	42	518	560
	480	2720	3200	120	680	800
RR = 1.19(162/960)/(318/2240)				RR = 4.33(78/240)/(42/560)		

Table 5. Relation of periodontitis to cardiovascular disease according to a hypothetical susceptibility factor that is simultaneously an effect modifier and a confounder

Cardiovascular Disease						
Susceptibility factor				No susceptibility factor		
Periodontitis	yes	no		yes	no	
Yes	200	600	800	40	360	400
No	200	1000	1200	160	1440	1600
	400	1600	2000	200	1800	2000
RR = 1.50(200/800)/(200/1200)				RR = 1.00(40/400)/(160/1600)		

dontitis and CVD as continuous variables were constructed through a linear regression model where the outcome diseases had separate independent variables and two independent variables that were common to both diseases (confounders). There is no effect modification in this example either, i.e. there are no product terms in the linear regression models through which the data were constructed. In our data set, CVD and periodontitis were classified so that CVD was given a prevalence of 15% and periodontitis 30%. We constructed 10% random variation in the simulated variables. The basic structure of the simulation data is presented in Fig. 2.

The data were generated using the SAS program and was analysed using the SAS GENMOD procedure, version 8.02. We analysed the data by using generalized linear models with a binomial distribution and a logit link function (logistic regression model).

The distributions of explanatory variables and the associations between explanatory variables and the outcome variable are presented in Table 6. The results showed that incomplete controlling of confounders (absence of one confounder) may induce spurious associations between periodontitis and CVD. In situations where both confounders were included in the model, the estimates were close to null association. Our simulations showed that restriction to the subgroups of a confounder eliminates the effects of confounding.

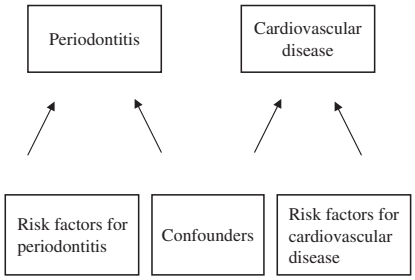

Fig. 2. Basic structure of the simulation data.

Discussion

Observational as well as interventional studies in periodontology may be confounded, or the relation between exposure (intervention) and outcome may be modified by extraneous factors. Potential confounders or effect modifiers include sex, age, bacterial burden and susceptibility factors, for example. As shown in our examples, uncontrolled confounding or partially controlled confounding may induce spurious associations between exposure and outcome. Depending on the magnitude of effect modification, it may be less of a concern than confounding (e.g. 2). However, if the magnitude of effect modification is unknown, it may have serious analytic implications.

Our examples as well as our simulation data are simple examples in many respects. Diseases are binomially distributed (Yes/No), and the number of explanatory variables is restricted. However, these examples resemble many epidemiological studies in the relation between periodontitis and systemic diseases, with smoking as a confounder in the sense that a moderate association is found in the total data, but not among the subgroup of never-smokers (Hujoel et al. 2002, Hyman et al. 2002). This discrepancy suggests that smoking is an important effect modifier or a confounder or both.

It is known that smoking is a risk factor for periodontitis and for many systemic diseases including CVD. However, attempts have seldom been made to control smoking otherwise than by using multivariate models, and often with very robust measurements of smoking. Previous studies strongly suggest that proper adjustment for smoking is not feasible when studying the relation between periodontitis and CVD. Most often, documentation of smoking, especially past smoking, is not complete. Individual factors including cultural, psychological and cognitive factors probably cause underreporting of smoking (Scott et al. 2001). Spiekerman et al. (2003) studied the reporting of current smoking by comparing serum cotinine measurements with self-reported smoking data, and they found that self-reported smoking underestimates current smoking. In addition to the fact that smoking history is subject to errors, smoking as a confounder has special features that may prevent controlling, namely that smoking history is difficult to conceptualize for any given purpose (Miettinen 1985, pp. 42–43, Hujoel et al. 2002). In these situations, it is possible that only restriction to the non-exposure category provides unconfounded results. Indeed, it should be used when appropriate adjustment for known confounders is not possible (Rothman & Greenland 1998, pp. 143–145, Miettinen 1999). However, restriction has several drawbacks, one notably being that the study offers a poor basis for generalizing the results. This may cause concern, if the relation under study is assumed to vary across the different categories of the extraneous determinant. On the other hand, a representative study and thus a homogeneous sample of the general population ''can produce unstable and hence ambiguous or even conflicting estimates across subgroups, and thus leave the very existence of the effect in doubt'' (Rothman & Greenland 1998, p.145).

In observational studies, heterogeneity in relation to the subjects' character-

Table 6. Associations between explanatory variables and outcome variable, proportions, odds ratios and their 95% confidence intervals (CI)

Explanatory variable	Proportion (%)	Cardiovascular disease odds ratios (95 % CI)*
No controlling		
Periodontitis†	29.9	2.17 (1.94–2.43)
Confounder one†	50.0	3.81 (3.36–4.32)
Confounder two†	30.0	3.62 (3.23–4.05)
Complete controlling (both confounders are controlled)		
Periodontitis†	29.9	0.99 (0.87–1.13)
Confounder one†	50.0	4.13 (3.61–4.74)
Confounder two†	30.0	3.94 (3.47–4.46)
Incomplete controlling (one confounder is controlled)		
Periodontitis†	29.9	1.56 (1.38–1.75)
Confounder one†	50.0	3.38 (2.97–3.86)
Stratification according to dichotomous confounder two		
Strata one		
Periodontitis†	50.5	1.00 (0.84–1.20)
Confounder one†	50.0	3.61 (3.00–4.35)
Strata two		
Periodontitis†	21.1	1.00 (0.83–1.21)
Confounder one†	50.0	4.90 (3.99–6.02)

*Mean value of the 1,000 simulations.
†Reference category: no disease or no risk.

istics causes a situation where confounding and/or effect modification are possible. Our example where the relation is modified by susceptibility factors resembles studies on aetiological factors of periodontitis. For example, differences in host response may explain why, in some people, the disease progresses rapidly to a more severe form while the progress is slower in other people. At present, knowledge about factors that modify the relation between aetiological factors and periodontitis is quite limited, but research has suggested that genetic predisposition could be an important susceptibility factor (Kinane et al. 2005). Previously, it has been estimated that genetic susceptibility accounts for about half the variation in periodontal disease (Michalowicz et al. 1991, 2000). On the other hand, genetic factors are not likely to be confounders in aetiological studies as they most likely are equally distributed between exposed and unexposed if the study is large enough and carried out in a relatively homogeneous population in relation to ethnic origin. In addition to aetiological studies, effect modification affects the results of intervention studies. For example, the effect of treatment may be observed in groups of individual with certain characteristics, for example, among non-smokers or among study subjects with good compliance. If trials are constructed in such situations in a heterogeneous population in relation to these characteristics, it is possible that the beneficial effects are not be found or shown with sufficient precision. It may also be the case that the invention may have a beneficial effect in one subgroup of patients, while it may have adverse effects in another subgroup.

All observational studies are at risk of yielding spurious associations as there is always some uncontrolled confounding related to an unmeasured common cause of which we are unaware (Robins 2001). In addition, there are factors such as health behaviours, especially smoking habits that are known and are measurable, but may still cause a substantial amount of confounding. The misclassification of confounders is a more serious problem than the misclassification of exposure or outcome variables, since the misclassification of exposure or outcome is usually a quantitative error attenuating the association, but misclassification of confounders causes a qualitative error leading to bias in either direction (Rothman & Greenland 1998, p. 133).

Our examples showed the risks for confounded estimates and consequently incorrect conclusions if effect modification is ignored or if uncontrolled confounding exists.

Most likely, the differences in the handling of confounders, including the measurement of confounders, and the ignoring of possible modifiers is one explanation for the variation in the results of the studies on the association between oral diseases and systemic diseases.

Acknowledgement

Pekka Ylöstalo wishes to thank the Finnish Dental Society for their financial support.

References

Greenland, S. & Brumback, B. (2002) An overview of relations among causal modelling methods. *International Journal of Epidemiology* **31**, 1030–1037.

Hujoel, P. P., Drangsholt, M., Spiekerman, C. & DeRouen, T. A. (2002) Periodontitis – systemic disease associations in the presence of smoking – causal or coincidental? *Periodontology* **30**, 51–60.

Hyman, J. J., Winn, D. M. & Reid, B. C. (2002) The role of cigarette smoking in the association between periodontal disease and coronary heart disease. *Journal of Periodontology* **73**, 988–994.

Kinane, D. F., Shiba, H. & Hart, T. C. (2005) The genetic basis of periodontitis. *Periodontology* **39**, 91–117.

Labriola, A., Needleman, I. & Moles, D. R. (2005) Systematic review of the effect of smoking on nonsurgical periodontal therapy. *Periodontology 2000* **37**, 124–37.

Merchant, A. T. & Pitiphat, W. (2002) Directed acyclic graphs (DAGs): an aid to assess confounding in dental research. *Community Dentistry and Oral Epidemiology* **30**, 399–404.

Michalowicz, B. S., Aeppli, D., Virag, J. G., Klump, D. G., Hinrichs, J. E., Segal, N. L., Bouchard, T. J. Jr. & Pihlstrom, B. L. (1991) Periodontal findings in adult twins. *Journal of Periodontology* **62**, 293–299.

Michalowicz, B. S., Diehl, S. R., Gunsolley, J. C., Sparks, B. S., Brooks, C. N., Koertge, T. E., Califano, J. V., Burmeister, J. A. & Schenkein, H. A. (2000) Evidence of a substantial genetic basis for risk of adult periodontitis. *Journal of Periodontology* **71**, 1699–1707.

Miettinen, O. S. (1985) *Theoretical Epidemiology. Principles of Occurrence Research in Medicine*. New York, NY: Wiley.

Miettinen, O. S. (1999) Etiologic research: needed revisions of concepts and principles. *Scandinavian Journal of Work, Environment & Health* **25**, 484–490.

Pernu, H. E., Pernu, L. M., Huttunen, K. R., Nieminen, P. A. & Knuuttila, M. L. (1992) Gingival overgrowth among renal transplant recipients related to immunosuppressive medication and possible local background factors. *Journal of Periodontology* **63**, 548–553.

Robins, J. M. (2001) Data, design, and background knowledge in etiologic inference. *Epidemiology* **12**, 313–320.

Rothman, K. J. & Greenland, S. (1998) *Modern Epidemiology*, 2nd edition. Philadelphia: Lippincott, Williams & Wilkins.

Scott, D. A., Palmer, R. M. & Stapleton, J. A. (2001) Validation of smoking status in clinical research into inflammatory periodontal disease. *Journal of Clinical Periodontology* **28**, 715–722.

Spiekerman, C. F., Hujoel, P. P. & DeRouen, T. A. (2003) Bias Induced by Self-reported Smoking on Periodontitis-Systemic Disease Associations. *Journal of Dental Research* **82**, 345–359.

Address:
Pekka Ylöstalo
Institute of Dentistry
University of Oulu
PL 5281
Oulu 90014
Finland
E-mail: Pekka.Ylostalo@oulu.fi

Clinical Relevance

Scientific rationale: The associations between periodontal and systemic diseases might be biased because of confounding. In addition, the relation might be modified by extraneous variables.

Principal findings: Our examples showed that incomplete controlling of confounders induces bias. Incomplete controlling of confounders and ignored effect modification may be responsible for the variation in results of studies on the association between oral and systemic diseases.

Practical implications: The presence of confounding and effect modification should be assessed. Where confounders cannot be controlled or effect modification cannot be assessed, restriction or stratification may provide unconfounded results.