

Does chronic periodontitis cause coronary heart disease?

A review of the literature

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The reported increases in the risk of developing coronary heart disease, or CHD, associated with chronic periodontitis, or CP, vary substantially from one study to the next ($P < .06$). Of the nine studies regarding this topic found in the medicodental literature¹⁻⁹ (Table), the maximum

The evidence to date supporting the chronic periodontitis-coronary heart disease association is weak.

CHD risk increase associated with CP was 169 percent¹; one study reported a 3 percent decrease.² If this substantial study-to-study heterogeneity were to be ignored, the summary of the nine studies of 94,869 people with 4,105 CHD events would suggest that CP increased CHD risk by 15 percent (95 percent confidence interval, or CI, 1.08 to 1.22).

This association is significant, and it may lead those who equate statistical significance with causality to suggest that the association is causal. However, because of the substantial heterogeneity

between studies—not only in reported risk estimates, but also in terms of how CP and CHD are defined—the calculation of a summary estimate is questionable. The causes and characteristics of these studies’ heterogeneity merit further investigation.

HOW STUDY CHARACTERISTICS AFFECT FINDINGS

“When you have eliminated the impossible, whatever remains, however improbable, must be the truth,” wrote Sir Arthur Conan Doyle. The best approach to discover the “truth” is not to prove a hypothesis, but to attempt to refute it, and to eliminate alternative explanations that

Background. Chronic periodontitis, or CP, has been associated with coronary heart disease, or CHD. This article reviews the available prospective CP-CHD evidence.

Literature Reviewed. In nine cohort studies, CP was associated with a 15 percent greater risk of developing CHD. Conclusions from individual studies depended on study characteristics. Summary risk estimates for studies controlling for smoking intensity (five of nine studies) or health awareness (two of nine studies) or studies with more than 600 CHD events (three of nine studies) suggest that CP is either not at all or weakly associated with CHD. Summary risk estimates for the studies that did not control for these factors or that examined an insufficient number of CHD events reported a weak increase in CHD risk associated with CP (20 percent greater). These data suggest that the CP-CHD associations observed in smaller studies are due to insufficient control for lifestyle differences. In addition, one cohort study reported that edentulous people had a CHD risk similar to that of people with CP. Therefore, the plausibility of dental infection elimination affecting CHD risk appears limited.

Summary. Current evidence supporting a causal CP-CHD link is weak. Rigorous methodological and analytical control of lifestyle factors such as smoking will be required to elucidate whether the CP-CHD disease association is either small or nonexistent.

Clinical Implications. Cigarette smoking destroys both oral and systemic health. Because of this strong common causal factor, oral and systemic health are linked. Dentistry should continue to play an important role in implementing smoking prevention and cessation programs.

may explain the observed associations.^{10,11} In Feynman’s words, “You should report everything that you think might make it (the hypothesis) invalid ... other causes that could possibly explain your results. In summary, the idea is to give all information.”¹²

TABLE

OVERVIEW OF NINE PROSPECTIVE COHORT STUDIES OF SUBJECTS WITH CHRONIC PERIODONTITIS, OR CP, ON THE LINK BETWEEN CP AND CORONARY HEART DISEASE, OR CHD.

STUDY	% RISK CHANGE (95% CI*)	CONTROL FOR SMOKING DOSE	CONTROL FOR HEALTH AWARENESS	SIZE OF RISK INCREASE	NO. OF CHD CASES
Mattila and colleagues²	+21 (8 to 36)	No	No	Small	52
Genco and colleagues¹	+168 (30 to 450)	No	No	Small to moderate	68
Beck and colleagues⁴	+50 (4 to 114)	No	No	Small	207
Hujoel and colleagues²	-3 (-28 to 31)	Yes	No	No association	352
Morrison and colleagues⁵	+37 (-20 to 135)	Yes	No	Small	466
DeStefano and colleagues⁷	+25 (6 to 48)	No	No	Small	556
Joshiyura and colleagues⁸	+4 (-14 to 25)	Yes	Yes	No association	757
Howell and colleagues⁹	+1 (-14 to 15)	Yes	Yes	No association	797
Hujoel and colleagues⁶	+13 (-5 to 34) [†]	Yes	No	Small	850

* CI: Confidence interval.

† The results presented here differ by 1 percent from those in the published report⁶ (1.13 vs. 1.14) because 14 subjects missed in the earlier analyses were included in the analyses performed for this article.

What alternative explanations beyond CP may explain the observed CP-CHD association? National U.S. survey data provide some clues to answer this question; people with and without periodontitis differ with respect to factors such as age, socioeconomic status, body mass index, smoking, psychological makeup, cholesterol levels, blood pressure and diabetes.⁶ Is it possible that studies reporting significant CP-CHD associations had insufficient control for these factors?

Following is a discussion of the impact of three factors—smoking dose, health awareness and sample size—on CP-CHD study conclusions.

Smoking dose. Controlling for smoking history is challenging. Consider the vitamin A–cancer association, for which a dozen case-control and cohort studies suggested that high consumption of carotenoids was associated with a reduced risk of lung cancer.¹³ Antioxidant vitamins in vegetables and fruits were believed to prevent carcinogenesis and atherogenesis by

interfering passively with oxidative damage to DNA and lipoproteins.¹⁴ Two large randomized, controlled trials refuted these epidemiologic findings and showed that vitamin A caused (instead of prevented) lung cancer.^{15,16} What went wrong? How did epidemiologic studies combined with biological plausibility lead to conclusions so inconsistent with randomized trial results?

One explanation is the lack of rigorous control for smoking history.¹⁷ As the rigor in controlling for smoking in one epidemiologic study¹⁷ increased, the vitamin A–lung cancer association switched from positive to negative. Crude adjustments for smoking history (classification of people as current, never- or former smokers) led to the dubious conclusion that vitamin A reduced the risk of lung cancer by 14 percent.¹⁷ In contrast, using the same data and the same analytic methodology but with more rigorous control for smoking history (taking into account smoking intensity, age at start of smoking and age at ces-

sation of smoking) led to the conclusion that high intake of vitamin A increased lung cancer risk by 12 percent.¹⁷ Rigorous control for smoking led to a conclusion that was consistent with the results of randomized controlled trials.¹⁷

To what extent have the nine cohort studies rigorously controlled for smoking? Currently, no CP-CHD study has had the same level of detailed (that is, rigorous) control for smoking history as the vitamin A–lung cancer research. A summary estimate of the five studies that adjusted somewhat for smoking dose^{2,5,6,8,9} suggests that periodontitis is not associated with CHD (relative risk, or RR, 1.05; 95 percent CI, 0.96 to 1.15). The summary estimate of the four studies that either did not adjust for smoking dose or adjusted poorly for smoking^{1,3,4,7} indicates a positive CP-CHD association (RR, 1.25; CI, 1.15 to 1.37). Lack of control for smoking history is a plausible explanation for the studies that reported significant CP-CHD associations.^{1,3,4,7}

Health awareness. Controlling for health awareness, or the interest in maintaining a healthy lifestyle, is more challenging. Unlike smoking—in which dose, duration and intensity of tobacco consumption can be quantified—no numbers can be attached to health awareness. Yet, health awareness may be equally important. People who do not have gingivitis may be more compliant with oral hygiene recommendations and may have higher health awareness than people who have gingivitis and periodontitis. Such differences in health awareness, when not controlled for, may induce spurious CP-CHD associations.¹⁸

Factors related to health awareness, such as compliance, have a significant impact on disease incidence. In a trial of clofibrate, a lipid-lowering drug, subjects compliant with use of the placebo had a 13 percent lower mortality rate than subjects who were not compliant with use of the placebo.¹⁹ In a trial of a chlorhexidine varnish aimed at lowering levels of *Streptococcus mutans* in the mouth, subjects compliant with use of the placebo varnish had a 29 percent lower caries rate than subjects not compliant with use of the placebo.²⁰ In both of these trials, a potential marker for health awareness (compliance with use of placebo) was a powerful indicator of health

outcomes. If periodontitis is a marker for poor plaque control and irregular dental care (that is, a lifestyle consistent with poor health awareness), then people with and without periodontitis will differ with respect to CHD incidence, not because of the periodontitis itself but because of the differences in health awareness and behavior.

Control for health awareness can be achieved by selecting populations with a similar educational and socioeconomic status, such as nurses, physicians or dentists. The two studies reporting on populations with similar health awareness^{8,9} reported no CP-CHD associations (RR, 1.02; 95 percent CI, 0.91 to 1.14). Studies in populations with a more heterogeneous health awareness (that is, representative samples of the U.S. population)¹⁻⁷ reported significant CP-CHD associations (RR, 1.21; 95 percent CI, 1.12 to 1.31). These contrasting findings suggest that incomplete control for health awareness may have led to significant CP-CHD associations.

Sample size. Positive results in small studies have a high chance of being false-positive results. Reasons for this trend include the lack of power, publication bias and “investigator’s enthusiasm.”²¹ Among the nine cohort studies located, a nonsignificant trend existed between the number of observed CHD events (directly proportional to power) and the reported CP-CHD association. The three smallest studies^{1,3,4} all reported significant CP-CHD associations; the second-smallest study,¹ which had no control for smoking or age and involved only 68 CHD events, reported the largest CHD risk increase: 169 percent. Among the six larger studies,^{2,5-9} only one⁷ reported a small (25 percent) yet significant CP-CHD association. Studies with more than 600 CHD events^{6,8,9} reported no CP-CHD associations (RR, 1.05; 95 percent CI, 0.96 to 1.15). Studies with fewer than 600 CHD events^{1-5,7} reported a 23 percent CHD risk increase (95 percent CI, 13 to 34 percent). Lack of power may have resulted in false-positive conclusions.

LIMITATIONS OF EPIDEMIOLOGY AND THE CHRONIC PERIODONTITIS—CORONARY HEART DISEASE ASSOCIATION

“People may think they have been able to control for things that are inherently not controllable,”

Factors related to health awareness, such as compliance, have a significant impact on disease incidence.

wrote Norman Breslow (cited in Taubes²²); this quote points to the central limiting factor of epidemiology: an inability to rigorously control for genetic and lifestyle factors, with a consequent inability to detect small risks. A certain amount of arbitrariness is involved in determining what epidemiologists typically mean by small risks, but the following quotations from clinical researchers, gathered by Taubes,²² provide some guidelines.

— Richard Doll, one of the founders of epidemiology: “No single epidemiological study is persuasive by itself unless the lower limit of its 95 percent confidence level falls above a threefold (200 percent) increased risk.”

— Dimitrios Trichopoulos, past chair of epidemiology at Harvard: “a fourfold (300 percent) increase [is] the lower limit.”

— Marcia Angell, former editor of *The New England Journal of Medicine*: “As a general rule of thumb, we are looking for a relative risk of 3 or more (> 200 percent increased risk) [before accepting a paper for publication].”

— Robert Temple, associate director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration: “My basic rule is if the relative risk isn’t at least 3 or 4 [a 200 percent or 300 percent increased risk], forget it.”

The size of the risk increase is one of the most important criteria by which epidemiologists judge causality, and the reported CP-CHD associations fall well below the limits of what is considered convincing. If the nine cohort studies had identified associations that fell above some generally accepted limit (for example, > 200 percent), the need for methodological rigor would have been less pressing. Under those circumstances, a more detailed adjustment for smoking or health awareness would have been unlikely to lead to different conclusions. However, since the nine cohort studies located for this review consistently identified small or no risk increases, methodological rigor is essential. Even small errors in the control for smoking history, health awareness or other lifestyle factors can induce biases that are substantially larger than the observed CP-CHD associations.²³

LETTING THE DATA GENERATE THE IDEA

“One must not verify an idea using the same data that suggested the idea in the first place ...”

Feynman²⁴ wrote. Commonly, when the results of a study are negative (disproving a thesis), investigators explore the data and “discover” associations that appear logical and believable, but that were not specified before the data collection (in other words, the data suggested the ideas). Such ideas are unreliable.

A textbook example regarding the unreliability of data-generated ideas is the research linking coffee drinking and pancreatic cancer. In the 1980s, a study was initiated to determine whether smoking caused pancreatic cancer.²⁵ The results were negative; smoking was found not to be associated with pancreatic cancer. Exploration of the data suggested the idea that coffee drinking was responsible for 50 percent of the pancreatic cancers in the United States.²⁵ However, when this idea was tested in a new study,

coffee drinking proved to be harmless. Ideas inferred from data (which is similar to betting on the horse after the race is over) are unreliable and need to be confirmed in other studies.²⁶

In the CP-CHD association, the data obtained have been used to suggest many ideas. For example, negative findings have led to the idea that causal associations do

exist for certain subgroups of the population such as people with pre-existing cardiovascular disease,²⁷⁻²⁹ women,³⁰ younger men³¹ or younger people.³² Another example: negative findings led to the idea that studies of people with self-reported periodontal disease or in whom periodontal disease was diagnosed based on Russell’s Periodontal Index³³ are too subjective to show associations. The challenge will be to confirm these data-generated ideas in studies other than “the one that suggested the idea in the first place.”

DO CHRONIC PERIODONTITIS TREATMENTS LOWER CORONARY HEART DISEASE RISK?

About 10 percent of fatal cancers may be caused by obesity.³⁴ Peto, the author of the study reporting this finding, indicated in an interview that this does not mean that weight loss programs should be recommended to lower cancer risk.³⁵ No evidence exists to support such a recommendation. Just because a causal characteristic or action produces an effect does not mean one should assume the opposite action would reverse an outcome.

‘One must not verify an idea using the same data that suggested the idea in the first place.’

Similarly, if convincing evidence regarding the CP-CHD link would come to light within the next few decades, it would not necessarily imply that CP treatments should be recommended to lower CHD risk (yet, this leap already has been made by some in the dental profession). At least some controlled evidence must be established first to suggest that CP treatments lower CHD risk.

Current evidence from two studies suggests that a complete, definitive and irreversible elimination of dental infections through full-mouth dental extractions does not lower CHD risk³⁶ or C-reactive protein serum levels, a potential mediator of CHD.³⁷ If a complete eradication of dental infections through full-mouth extractions does not provide benefits (and possibly worsens oral health and nutrient intake), why would partial and temporary elimination of infection (in the form of periodontal treatments) provide a CHD-mediating benefit to the patient? Treatment recommendations should be based on controlled evidence, not biological plausibility.

LOGICAL SIMPLICITY AND BIOLOGICAL PLAUSIBILITY

Periodontitis has been inconsistently associated with the diseases that are caused by smoking: coronary heart disease,¹⁸ stroke,³⁸ chronic obstructive pulmonary disease,³⁹ malignant neoplasm of the lung,⁴⁰ low birth weight,⁴¹ osteoporosis and diabetes. Providing a unifying and biologically plausible causal explanation for this portfolio of systemic diseases associated with periodontitis is difficult. Different mechanisms have been proposed, and it is unclear which ones are plausible.¹⁸ Bacteremia, which occurs with eating, defecating, brushing, breathing, flossing, sex, insect bites and skin scrapes, has been suggested as one culprit. Why periodontal bacteremia in particular would be harmful is unclear.

Interestingly, 8 to 20 square centimeters of periodontal pocket tissue⁴² have been described in the medicodental literature as “an endocrine organ secreting inflammatory mediators.”⁴¹ Why other systemic inflammatory diseases, such as rheumatoid arthritis, are not associated with an increased CHD risk is unclear. How either the periodontal “endocrine organ” or the periodontal bacteremia can generate such diverse diseases as cancer, diabetes and CHD is unexplained. Providing a unifying biologically plausible causal explanation consistent with current evidence is challenging and is currently not possible.

In contrast, a unifying and biologically plausible noncausal explanation for these associations is simple: inadequate control for smoking and associated lifestyle factors spuriously induced periodontitis–systemic disease associations. Current epidemiologic evidence, including the lack of a beneficial CHD effect of dental infection elimination, is consistent with such an explanation.

CONCLUSION

The evidence to date supporting the CP-CHD association is weak. This conclusion is concurrent with two overviews that used different criteria for causality and different study selection criteria.^{18,43} While there is evidence that acute dental infections, particularly of lower molars, can be fatal,⁴⁴ there is no convincing evidence that CP affects CHD risk. What has been convincingly demonstrated is that large cohorts with rigorous control for alternative explanations such as lifestyle (most importantly smoking) and genetics will be required to elucidate whether the etiologic role of chronic dental infections in CHD is small or nonexistent. ■

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