

The relationship between oral conditions and ischemic stroke and peripheral vascular disease

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The major epidemiologic studies investigating the association between oral conditions (disease and tooth loss) and systemic diseases such as cardiovascular disease, or CVD, were reviewed in 2000.¹ On the basis of causal criteria, the overall evidence regarding the periodontal-systemic association is not strong, and the associations

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may or may not be causal.¹ Several studies, including many longitudinal studies, have assessed whether or not an association exists between periodontal disease and CVD (for example, coronary heart disease, or CHD; stroke; and peripheral vascular disease).²⁻¹¹ Many of these same cohorts also have been evaluated in terms of the association between tooth loss and cardiovascular disease.

The association between periodontal disease and CHD has been reviewed extensively in the literature¹²⁻¹⁴ and by Hujoel in his article, "Does Chronic Periodontitis Cause Coronary Heart Disease? A Review of the Literature," on page 31S of this supplement to JADA. The results to date are inconsistent. There is insufficient evidence to establish a causal relationship between periodontal disease and CHD; there are even fewer studies linking tooth loss with CHD. More importantly, the independence of these associations from confounding factors has

Background. This article is a critical review of the epidemiologic studies linking or disassociating oral conditions with stroke and peripheral vascular disease, or PVD. It also describes possible causal and non-causal pathways for these associations.



Types of Studies Reviewed. The author reviewed studies that evaluated the oral conditions of periodontal disease or tooth loss as risk factors for arterial disease and stroke.

Results. Seven of nine studies evaluating tooth loss and periodontal disease as risk factors for stroke or PVD showed some significant associations. The studies varied in the exposures and outcomes evaluated; therefore, the associations were not consistently replicated. It is unclear whether the associations found between these oral conditions and cardiovascular disease had any causal component. In the absence of any causal relationship, the associations may be explained by common risk factors. Alternatively, there may be a causal relationship that may be explained by one or more potential causal pathways. Further epidemiologic studies are needed, and the role of nutrition and other inflammatory mediators needs to be explored further in this context.

Clinical Implications. It is recommended that clinicians continue to provide standard professional care, as well as nutritional counseling to help patients maintain a healthy diet after extractions. Clinicians are cautioned against suggesting extractions as a means of preventing cardiovascular disease.

not been consistently established; thus, it is possible that these associations may be partly or completely explained by risk factors common to oral and cardiovascular disease.

This article focuses on reviewing the studies that have looked for associa-

tions between oral conditions and stroke and peripheral vascular disease, or PVD, and discusses causal and noncausal explanations for these associations.

STROKE

A stroke is damage to the brain due to a reduction in the blood supply to the brain. When a blood vessel that delivers oxygen and nutrients to the brain is obstructed, the condition is called an ischemic stroke, or cerebral ischemia. Hemorrhagic stroke occurs when a blood vessel supplying the brain bursts and causes bleeding into the brain. In any stroke, the nerve cells in the affected area of the brain can become deprived of oxygen and die within minutes of onset of the stroke. Therefore, a stroke can cause an impairment of body functions—such as speech, memory and movement—that are controlled by the affected portion of the brain. Obviously, a stroke can be a debilitating event. The risk factors for stroke include smoking, high blood pressure, diabetes and CVD.

Periodontal disease, tooth loss and stroke. Two case-control studies^{15,16} and five longitudinal studies^{6,7,9-11} evaluated the association between periodontal disease and stroke, and four of the longitudinal studies^{6,9-11} also evaluated the association between tooth loss and stroke (Table).

Nonischemic stroke—that is, hemorrhagic stroke—has a different etiology, and is not generally associated with dental or other infections. The study that evaluated hemorrhagic stroke separately found null associations between it and any type of infection.⁹ Hence, it is important to evaluate ischemic stroke separately.

The outcome is somewhat different across the reported studies, ranging from total stroke⁷ to fatal stroke,¹⁰ nonfatal stroke¹¹ and ischemic stroke.^{6,9,15} The first report on stroke was a case-control study. Syrjanen and colleagues¹⁵ evaluated 40 cases of ischemic stroke and 40 randomly selected community control subjects matched for sex and age. They found significant associations between stroke and subgingival calculus, suppuration in the gingival pocket, and a dental pantomographic index score, but no association with Total Dental Index score. (The score ranges from zero to 14, with zero indicating no disease. The score increases with increasing levels of caries,

periodontitis, periapical lesions, nonvital teeth and pericoronitis.) The analysis did not control for smoking or any other confounders, so it is hard to interpret the results.

Another more recent case-control study by Grau and colleagues¹⁶ evaluated the association between similar dental indexes and ischemic stroke. Among 166 cases and 166 age- and sex-matched control subjects, poor dental status (defined by the authors as Total Dental Index score ≥ 6) was associated with an odds ratio of 2.6. The analysis controlled for age, sex, social status, diabetes, current smoking and pre-existing vascular disease. The authors found a significant association between ischemic stroke and periodontitis and periapical lesions (but not caries, nonvital teeth or pericoronitis); however, the analyses did not control for several confounders such as past smoking, number of cigarettes smoked, obesity and physical activity.

All five longitudinal studies excluded people who had CVD before the baseline examination, which is necessary to establish a time sequence for oral conditions predating CVD.

The study by Beck and colleagues⁷ compared men who had had any type of stroke with men who did not develop CVD during the follow-up. They found a significant association between periodontal disease and total stroke: relative risk, or RR, of 2.80.

The study by Wu and colleagues⁹ found a positive association between periodontal disease and ischemic stroke (RR = 2.11); the risk was even higher when limited to fatal stroke. Slightly smaller RRs were found for edentulism that were significant for fatal ischemic stroke. The researchers found no association between periodontal disease and hemorrhagic stroke.

Morrison and colleagues¹⁰ found a smaller non-significant association between periodontal disease and total fatal stroke (RR = 1.63), and a similar association between periodontal disease and edentulism.

In preliminary analyses from the Health Professionals Follow-up Study, or HPFS, Joshipura and colleagues⁶ found small associations between periodontal disease history at baseline or during the follow-up and ischemic stroke (RR = 1.27), and between fewer teeth at baseline and

It is possible that the association between periodontal disease and stroke is limited to recent disease.

TABLE

SUMMARY OF STUDIES EVALUATING THE POTENTIAL RELATIONSHIP BETWEEN ORAL CONDITIONS AND STROKE.									
STUDY AUTHORS	N*	POPULATION ORIGIN/TYPE	YEARS OF FOLLOW-UP	BASELINE EXCLUSIONS	EX-POSURE	OUT-COMES	RELATIVE RISK	CONFIDENCE INTERVALS	CONFOUNDERS CONTROLLED†
Relationship Between Periodontal Disease and Stroke									
Syrjanen and colleagues¹⁵	80	Helsinki, Finland	N/A‡	N/A	Composite dental index score	Nonfatal ischemic stroke	<i>P</i> < .05	N/A	<i>Age and sex</i>
Grau and colleagues¹⁶	332	Germany	N/A	N/A	Composite dental index score	Nonfatal ischemic stroke	Odds ratio 2.6	(1.18 to 5.70)	Current smoking; diabetes mellitus, or DM; socioeconomic status, or SES; pre-existing vascular disease; age; sex
Beck and colleagues⁷	1,147	U.S. military veterans	18	N/A	Mean bone loss > 20% of root	Total stroke	2.80	(1.45 to 5.48)	Age; smoking (current, former, never); non-insulin-dependent DM; diastolic blood pressure, or BP; family history; education; sex
Morrison and colleagues¹⁰	10,120	Nutrition Canada Survey	20	Prior coronary heart disease, or CHD	Obvious pockets or loose teeth	Total fatal stroke	1.63	(0.72 to 3.67)	Age; sex; serum total cholesterol level; smoking (never, former, current: < 1 cigarette/day, 1-20 cigarettes/day, > 20 cigarettes/day); DM; hypertensive status, province of residence
Wu and colleagues⁹	9,962	NHANES I§	14	Prior CHD; congestive heart failure, or CHF; stroke; cancer	Score on Russell's Periodontal Index (four or more teeth with overt pockets)	Ischemic stroke; hemorrhagic stroke; fatal ischemic stroke	2.11 1.22 2.90	(1.30 to 3.42) (0.53 to 2.63) (1.49 to 5.62)	NHANES I design features; sex; race; age; education; poverty level; DM status; hypertension; smoking (current, former, never); alcohol use; body mass index, or BMI; serum cholesterol level
Howell and colleagues¹¹	22,037	Physicians	12.3	Prior myocardial infarction, or MI; transient ischemic attack, or TIA; stroke; cancer	History of periodontal disease	Total nonfatal stroke	1.01	(0.81 to 1.27)	Age; randomization arm (aspirin and/or beta carotene); DM; hypertension; diastolic BP; treatment for high BP; BMI; smoking status (never, former, current: < 20 cigarettes/day, ≥ 20 cigarettes/day); alcohol use; physical activity level; angina; parental history of MI; sex; SES; health behavior
Joshi-pura and colleagues⁶	44,116	Health professionals	10	Prior cardiovascular disease, or CVD; diabetes	History of periodontal disease at baseline; periodontal disease history at baseline or during follow-up	Ischemic stroke	NS¶ 1.27	(1.01 to 1.61)	Age; smoking status, including amount smoked; obesity; alcohol use; amount of exercise; family history of CVD; employment in dental profession; baseline reported hypertension and hypercholesterolemia; DM; sex; SES; health behavior

* N: Number.
† Confounders controlled are the confounders explicitly included in the reported analysis, and in italics are the confounders controlled by restriction or matching.
‡ N/A: Not available.
§ NHANES I: The First National Health and Nutrition Survey (1971-1975).
¶ NS: Not significant.

ischemic stroke (RR = 1.38 for ≤ 24 vs. 25 or more teeth).

The Physicians' Health Study, or PHS,¹¹ and HPFS are similar in design and population. While both are restricted to a homogeneous socioeconomic population, the two studies show contradictory results. The HPFS found an association between recent periodontal disease, baseline number of teeth and ischemic stroke, whereas the PHS found no such associations. There are several possible explanations for this.

To begin with, the PHS only had data on tooth loss during the year preceding the baseline examination. A similar measure of tooth loss the year preceding the baseline examination was not reported in the HPFS abstract. Tooth loss during the preceding year in the PHS may be a marker of good systemic health, as extraction is an elective procedure and people with poor systemic health may choose not to undergo what they might view as an unnecessary procedure.

Next, the PHS evaluated incidence of total

TABLE

SUMMARY OF STUDIES EVALUATING THE POTENTIAL RELATIONSHIP BETWEEN ORAL CONDITIONS AND STROKE (CONTINUED).

STUDY AUTHORS	N*	POPULATION ORIGIN/TYPE	YEARS OF FOLLOW-UP	BASELINE EXCLUSIONS	EXPOSURE	OUT-COMES	RELATIVE RISK	CONFIDENCE INTERVALS	CONFOUNDERS CONTROLLED†
Relationship Between Tooth Loss and Stroke									
Morrison and colleagues¹⁰	10,120	Nutrition Canada Survey	20	Prior CHD	Edentulism	Fatal stroke	1.63	(0.77 to 3.42)	Age; sex; serum total cholesterol; smoking status (never, former, current: < 1 cigarette/day, 1-20 cigarettes/day, > 20 cigarettes/day); DM; hypertensive status; province of residence
Wu and colleagues⁹	9,962	NHANES I	14	Prior CHD, CHF, stroke, cancer	Edentulism vs. no gingivitis/periodontal disease	Ischemic stroke; fatal stroke	1.41 2.12	(0.96 to 2.06) (1.14 to 3.95)	NHANES I design features; sex; race; age; education; poverty level; DM status, hypertension; smoking; alcohol use; BMI; serum cholesterol level
Howell and colleagues¹¹	22,037	Physicians	12.3	Prior MI, TIA, stroke, cancer	Tooth loss during follow-up	Nonfatal stroke	1.07	(0.91 to 1.27)	Age; randomization arm (aspirin and/or beta carotene); DM; hypertension; diastolic BP; treatment for high BP; BMI; smoking status (never, former, current: < 20 cigarettes/day, ≥ 20 cigarettes/day); alcohol use; physical activity level; angina; parental history of MI; sex; SES; health behavior
Joshiyura and colleagues⁶	44,116	Health professionals	10	Prior CVD, diabetes	< 24 teeth vs. 25 or more teeth	Ischemic stroke	1.38	(1.10 to 1.75)	Age; smoking status, including amount smoked; obesity; alcohol use; amount of exercise; family history of CVD; employment in dental profession; baseline reported hypertension and hypercholesterolemia; DM; sex; SES; health behavior

* N: Number.
 † Confounders controlled are the confounders explicitly included in the reported analysis, and in italics are the confounders controlled by restriction or matching.
 ‡ N/A: Not available.
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nonfatal stroke, whereas HPFS evaluated fatal and nonfatal ischemic stroke.

Another explanation could be that only a small number of teeth are lost in a single year; hence the variation in tooth loss over the past year in the PHS is small compared with the baseline number of teeth in the HPFS.

Meanwhile, the HPFS evaluated periodontal disease history and recent periodontal disease during the follow-up; an association was found with recent periodontal disease, but not with historic periodontal disease. The PHS evaluated only past periodontal disease and did not find an association. Hence, it is possible that the association between periodontal disease and stroke is limited to recent disease.

In a comparison of the studies that evaluated both periodontal disease and tooth loss in the same cohort,^{6,7,9-11,15,16} it appears that the association between tooth loss and stroke is similar to the association between periodontal disease and stroke. My interpretation of the literature is that

- it is possible that both of these associations may be explained by common risk factors;
- tooth loss is as likely as periodontal disease to be an independent risk factor;
- dentists should be cautioned against extracting teeth on the basis of preventing CVD.

All studies I reviewed for this article show an association between oral conditions and increased risk of experiencing stroke, other than the PHS, which shows no association. Although several studies show an association between tooth loss/periodontal disease and stroke, no two studies are consistent in defining the outcome and exposure. Hence, no association has been truly replicated. It is difficult to rule out residual confounding variables, as there are several common risk factors. The longitudinal studies controlled for most major confounders, although there still is room for greater rigor. Incomplete control for smoking, blood pressure or healthy behavior may explain some of the positive associations.

PERIPHERAL VASCULAR DISEASE

Peripheral vascular disease, or PVD, is caused by diminished blood flow to the extremities. The symptoms include intermittent claudication; extreme cases could lead to disability and amputation. Only two studies have reported on the relationship between oral conditions and PVD.

The first study by Mendez and colleagues⁸ was conducted as part of the Veterans Affairs Dental Longitudinal Study among 1,110 male veterans. During a 25-year follow-up period, 80 men developed PVD. Men with periodontal disease (defined as mean bone loss > 20 percent of the root surface) had a 2.3 times higher risk of incidence of PVD vs. men without periodontal disease (odds ratio, or OR, = 2.27; 95 percent confidence interval, or CI, = 1.32 to 3.90).

The second report is an abstract from the Health Professionals' Follow-up Study.¹⁷ During a 10-year follow-up period, 400 cases of PVD were recorded. Among 45,167 male health professionals, those who lost one or more teeth during the follow-up period had a relative risk of 1.33 (95 percent CI = 1.05 to 1.68) of experiencing PVD compared with men who did not lose any teeth during the follow-up period. Participants who had myocardial infarction, stroke, PVD or cancer before the baseline examination were excluded to establish temporality.

Both these studies controlled for standard CVD confounding factors. To my knowledge, are there no other published studies on this subject. Hence, we do not know if further studies will corroborate or conflict with these positive associations. Based on the literature to date, it seems plausible that there may be an independent association between oral conditions and risk of experiencing PVD. Several well-conducted longitudinal studies corroborating these results are needed before interpreting a causal relationship.

THE RELATIONSHIP BETWEEN ORAL CONDITIONS AND CARDIOVASCULAR DISEASE: POSSIBLE PATHWAYS

The associations relating oral conditions with CVD may be explained by causal or noncausal pathways or some combination of the two.

Noncausal pathway. *Common risk factors/*

confounders. Common risk factors (factors related to exposure and outcome) could lead to an observed association in the absence of a causal association. Common risk factors for oral conditions and CVD include age, smoking/alcohol use, health behaviors/habits, genetic disposition, socioeconomic status, stress, obesity, diet, physical activity, access to care and diabetes mellitus. Nutrition also could be a confounder, as nutritional factors (alcohol use, vitamin C intake, sugar intake and so forth) and body weight may be related to oral conditions and, independently, to CVD. In evaluating causal pathways, confounders should be controlled first by restriction or matching, or should be adjusted in the analyses. Using certain populations such as health professionals inherently controls for socioeconomic status and healthy behavior, factors that otherwise are difficult to measure or control,

because such populations consist of a homogeneous group of people. Health professionals generally have a higher health awareness, practice healthier behavior and thus are much more homogeneous with respect to healthy behavior than is the general population.

Since oral and cardiovascular disease have many factors in common, it is important to rule these out as alternative explanations before interpreting a relationship as causal. The studies described in this article controlled for several common factors. How-

ever, important factors—including smoking, socioeconomic status, obesity, exercise, genetic predisposition, diet and blood pressure—have been incompletely controlled for in many studies. Therefore, until we have several studies showing consistent associations after being well-controlled for potential confounders, common risk factors are likely explanations for these associations.

Validity of outcome measures. Stroke generally was assessed using some combination of self-report, medical records and other information from subjects' records. Stroke either was evaluated as total stroke or was separated into ischemic stroke (which is more relevant in the context of this discussion) and hemorrhagic stroke. The variation in the type of stroke evaluated may explain some of the variation in the results across different studies.

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Pathways Relating Oral Conditions With Cardiovascular Disease

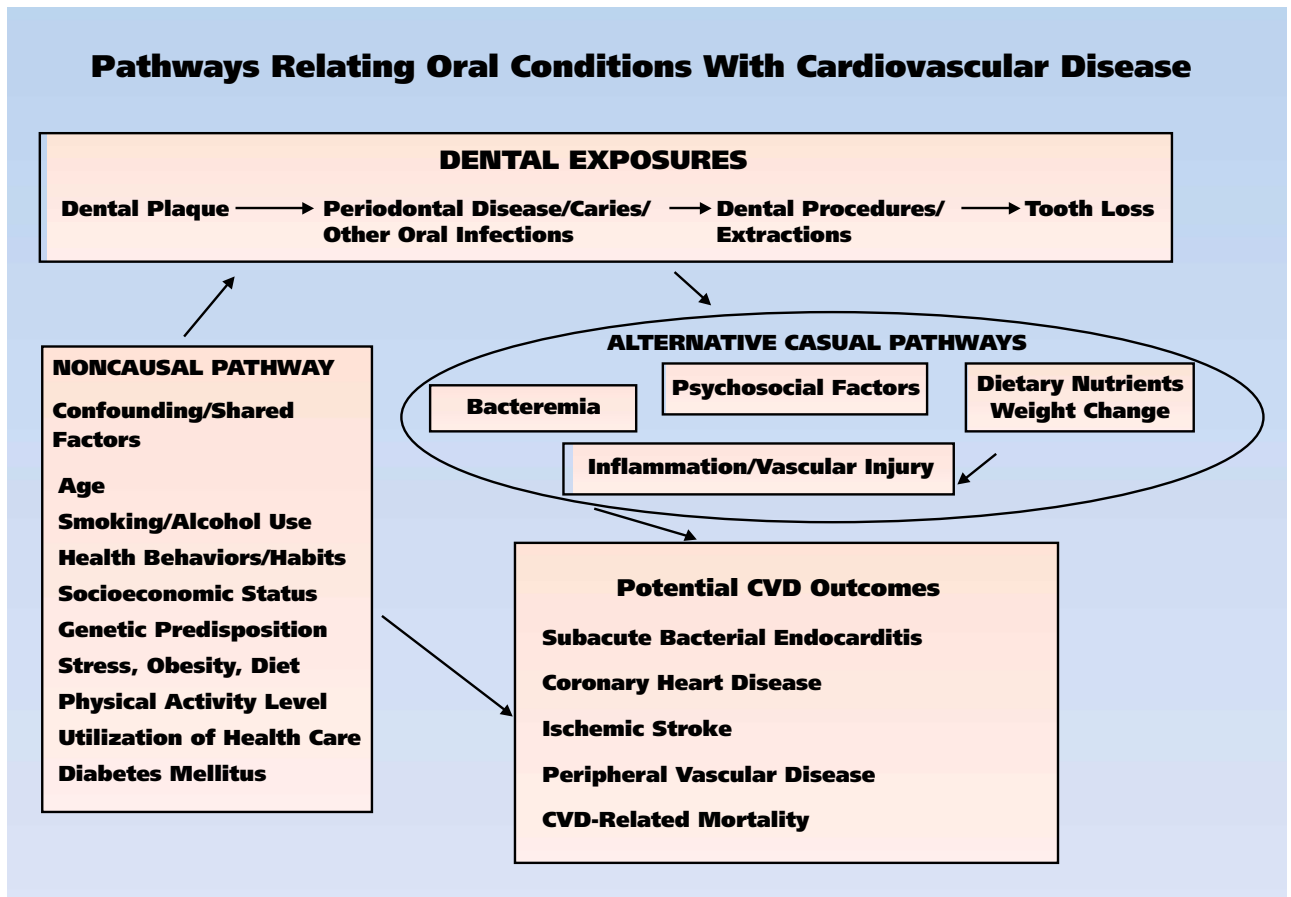


Figure. Pathways relating oral conditions with cardiovascular disease, or CVD. Adapted with permission of the publisher from Joshipura and colleagues.¹

Validity of exposure. Number of teeth or tooth loss is expected to be well-reported in most U.S. populations. All studies use different measures of periodontal disease; there is no standard, universally accepted measure for classifying people with or without periodontal disease. Studies have used varying measures of periodontal disease, bone loss, attachment loss, Russell's Periodontal Index and validated self-reported measures of periodontal disease history among dentists and other health professionals. Clinical studies vary from study to study in specifying cutoffs for defining people as having periodontal disease. Although clinical measures are reasonably well-accepted in research, there is no standard cutoff; hence, the reports may be biased toward cutoffs that show positive associations.

Another limitation of clinical measures is that one cannot measure antecedent periodontal disease among the teeth that have been extracted; it may be that extracted teeth had even worse periodontal disease. On the surface, self-reported mea-

asures seem more limited, but they have been validated against radiographs¹⁸ and also show anticipated associations such as those with age, diabetes and smoking among special groups (for example, health professionals).¹⁹ Self-reported measures also have the advantage of being a cumulative measure of periodontal disease that includes periodontal disease in the extracted teeth, which is not captured in clinical measures evaluated at a single point in time. Although none of the measures is perfect, they all compare well against measures in areas such as nutrition and psychiatry, in which correlations of 0.4²⁰ have been considered acceptable measures and have been used in etiologic studies reported in the most prestigious journals.^{21,22}

CAUSAL EXPLANATIONS

Relationship between caries, periodontal disease/tooth loss and CVD. As shown in the figure, periodontal disease or caries generally precedes tooth loss. It is important to note that one

could observe an association between tooth loss and stroke, but it may be explained by antecedent periodontal disease or caries. Alternatively, one could observe an association between periodontal disease and stroke, but it may be explained by tooth loss and diet. Hence, it is important to evaluate periodontal disease, tooth loss and CVD simultaneously to understand these interactions. In the HPFS study on stroke,⁶ when the researchers evaluated periodontal disease and tooth loss simultaneously to assess whether tooth loss was a mediator of the periodontal disease–stroke association, they found that periodontal disease no longer was significant whereas tooth loss was, suggesting that tooth loss may be part of the pathway.

Pathways relating periodontal disease and CVD—including bacteremia, inflammation and vascular injury—have been discussed in detail in many review articles.^{1,7,12} There are few reports in the literature directly linking caries with CVD. Hence, the role of caries is unclear.

Other causes. It is conceivable that some factor related to the extraction process—*anxiety, stress, depression and impact on social behavior and relationships during or after tooth loss*—also could play a role.²¹ These factors need to be explored further.

Nutrition: a potential mediator. Tooth loss could lead to reduced masticatory capacity, which in turn could lead to a diet that may be detrimental to health. As a result, dietary factors such as reduced fiber and fruit intake or increase in saturated fat intake could be mediators in the tooth loss–CVD associations.^{23,24} Similarly, periodontal disease, impaired dentition or tooth loss could cause weight change, possibly leading to CVD.¹

A recent report linking periodontal disease and obesity also is interesting.²⁵ The impact of periodontal disease on nutritional intake and weight warrants further research. In addition, nutrients could affect host response to inflammation; nutritional mediators may interfere with inflammatory cytokine activity, affect immune function and inflammatory markers and, possibly, affect both oral health and the development of systemic disease.^{26,27} It is possible that nutrition may play a role in the periodontal disease–CVD association.

CONCLUSIONS

The studies to date suggest that oral conditions may be associated with increased risk of ischemic stroke and peripheral vascular disease; however, more well-conducted studies are needed to show consistency of these associations. It is not clear at this stage whether the association between periodontal disease/tooth loss and CVD has any causal component. Clinicians are cautioned not to overstate these associations.

Further studies are needed to corroborate the associations between oral conditions and stroke and PVD. Much more work is needed to rule out confounders as an explanation for the associations, and to evaluate inflammatory and dietary mediators of these associations.

Educating patients in improving personal oral hygiene and self-care and in the importance of adequate professional care is beneficial regardless of the relationship with systemic disease. Patients undergoing extractions would benefit from well-fitting prostheses that will enable them to chew various foods. Clinicians are recommended to provide nutrition counseling to help patients maintain a healthy diet after extractions, even if their masticatory efficiency is slightly reduced. Whether dental procedures such as periodontal surgery or extraction of teeth are beneficial or harmful with respect to the risk of developing CVD is unknown, and has never been directly evaluated. The literature to date suggests that people who have had more extractions—that is, those with fewer teeth—are at increased risk of developing CVD. Hence, clinicians are cautioned not to suggest extractions as a means of preventing CVD. ■

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