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AHA SCIENTIFIC STATEMENT

Periodontal Disease and Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association

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ABSTRACT: Since the publication of the 2012 American Heart Association scientific statement on the association between periodontal disease and atherosclerotic cardiovascular disease, the body of literature on this topic has grown substantially. Atherosclerotic cardiovascular disease is the leading cause of death globally, and understanding contributors and potential targets to decrease this risk is paramount. This updated scientific statement synthesizes new evidence concerning an association between periodontal disease and atherosclerotic cardiovascular disease, including findings from Mendelian randomization studies, interventions targeting periodontal disease, and studies exploring systemic markers, such as inflammatory cytokines and vascular measures. The scientific statement also highlights disparities in the prevalence of periodontal disease, particularly among underresourced populations; explores potential mechanisms linking periodontal disease with cardiovascular outcomes through direct pathways, such as bacteremia, and indirect pathways, such as chronic systemic inflammation; and identifies areas needing further clarification that would benefit from additional research.

Key Words: AHA Scientific Statements ■ atherosclerosis ■ coronary disease ■ inflammation ■ myocardial infarction ■ periodontal diseases ■ stroke

Atherosclerotic cardiovascular disease (ASCVD) is the most common cause of death globally, with considerable resources invested worldwide to treat its complications. In the United States, heart disease and stroke account for more deaths each year than cancer and chronic lower respiratory disease combined, and the cost of heart disease to society was $407.3 billion in 2018 through 2019.[1] Determining risk factors for ASCVD and effective preventive measures and interventions are key to addressing this important health issue.

The body of literature showing possible associations between periodontal disease and ASCVD has been increasing. Several mechanisms appear to potentially explain this association, including bacteremia, vascular infection, and systemic inflammation.[2,3] Effective prevention and treatment of periodontal disease could potentially decrease ASCVD burden.

A previous American Heart Association scientific statement, published in 2012, found that data supported associations between periodontal disease and ASCVD but noted the need for more robust evidence regarding clinical outcomes and the effect of treating periodontal disease on ASCVD outcomes.[4] The goal of this scientific statement is to highlight updated literature and understanding of the potential effect of periodontal disease on ASCVD, the mechanisms behind the association, and the benefit of treating periodontal disease on ASCVD outcomes. A Supplemental Table is provided regarding language used when discussing associations. In addition, proposed effects of periodontal disease on

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vascular health are examined beyond associations with atherosclerosis.

DEFINITION AND EPIDEMIOLOGY OF ASCVD AND PERIODONTAL DISEASE

Definition of ASCVD

ASCVD encompasses chronic conditions resulting from plaque formation in blood vessel walls, including ischemic heart disease, cerebrovascular disease, and peripheral vascular disease, which can result in acute clinical events, including acute coronary artery disease (CAD), myocardial infarction (MI), and stroke.

Epidemiology of ASCVD

ASCVD is the most common cause of death in the United States, accounting for ≈30% of all deaths.[1] Deaths due to ASCVD have increased over the past decade, with ≈928 713 deaths caused by ASCVD recorded in 2020. Coronary heart disease is the most common cause of ASCVD-related deaths, accounting for half of ASCVD-related deaths between 1990 and 2019. An estimated 605 000 new heart attacks and 200 000 recurrent attacks occur each year. In addition, ≈795 000 people annually experience a new or recurrent stroke. Strokes accounted for ≈1 of every 21 deaths in the United States in 2020 and ranks fifth among all causes of death. Atherosclerotic lower-extremity peripheral artery disease is estimated to affect 5.8% to 10.7% of the US population >40 years of age. Overall, ASCVD presents enormous disease burden and societal impact.

Definition of Periodontal Disease

Periodontal disease is a multifactorial chronic inflammatory disease (Figure 1).[5] Periodontal disease typically begins with dental plaque biofilm–induced gingival inflammation and bleeding, and progresses to loss of clinical attachment, possible gingival recession, deepening of periodontal pockets, and destruction of tooth-supporting alveolar bone (Figure 2). Severe periodontitis results in tooth mobility, tooth loss, and masticatory dysfunction that can affect nutrition, quality of life, and social well-being. Periodontal disease classification includes 4 forms: necrotizing periodontal diseases, periodontitis, periodontitis as manifestation of systemic diseases, and periodontal abscesses and endodontic–periodontal lesions. Periodontitis is staged on the basis of severity and complexity of management, ranging from initial to severe disease with potential loss of dentition, and by its extent and distribution (eg, localized, generalized, molar–incisor distribution), and graded on the basis of rapidity of progression.[6]

Epidemiology of Periodontal Disease

Analysis of a US national periodontitis surveillance project estimated that 42% of dentate US adults ≥30 years of age had periodontitis—7.8% with the severe form.[7] Kassebaum et al[8] conducted a systematic review of 72 studies from 37 countries and estimated a global age-standardized prevalence of severe periodontitis of 11.2%, with prevalence increasing with age and varying by region. Estimates from the 2019 Global Burden of Disease study suggest 1.1 billion prevalent cases globally, with age-standardized rates increasing 8.44% between 1990 and 2019, largely driven by global population growth.[9]

Impact of Health Disparities on ASCVD and Periodontal Disease

The burden of severe periodontitis is higher among individuals from underdeveloped countries and regions globally[9] and among US adults >65 years of age, Mexican American individuals, non-Hispanic Black individuals, and smokers. The prevalence rises with increasing poverty levels, reaching 60% among individuals earning <100% of the federal poverty level.[7]

MECHANISMS FOR ASSOCIATION OF PERIODONTAL DISEASE AND ASCVD

Although periodontal disease and ASCVD share common risk factors, such as advanced age, smoking, male sex, low physical activity, overweight or obesity, low socioeconomic status, and low educational level, new evidence also indicates an independent association between periodontal disease and ASCVD through direct and indirect mechanisms.[2,10,11] Despite a lack of conclusive epidemiologic data to support causality, these mechanisms suggest an independent association.

Direct mechanisms of the association are thought to be through bacteremia and vascular infection. Dental plaque in periodontal disease contains multiple bacterial strains.[2,3] Periodontal pockets, with manipulation of the tissue, can result in bleeding, which allows periodontal bacteria to enter systemic circulation.[3] Once in the bloodstream, pathogens can trigger a systemic inflammatory response.[2,12,13] This, along with increased vascular permeability, could lead to endothelial dysfunction. Endothelial dysfunction can be a sign of early subclinical atherosclerosis.[14–16] Bacteremia from chronic periodontal infections may increase the inflammatory burden that accelerates atherogenesis.[2,3,17] Inflammation due to direct oral microbiome actions may affect systemic inflammation of blood vessel walls through 2 modes: direct invasion of bacteria through the diseased and inflamed periodontal tissues into the general circulation and phagocyte-mediated bacterial translocation. The oral microbiome thereby invades

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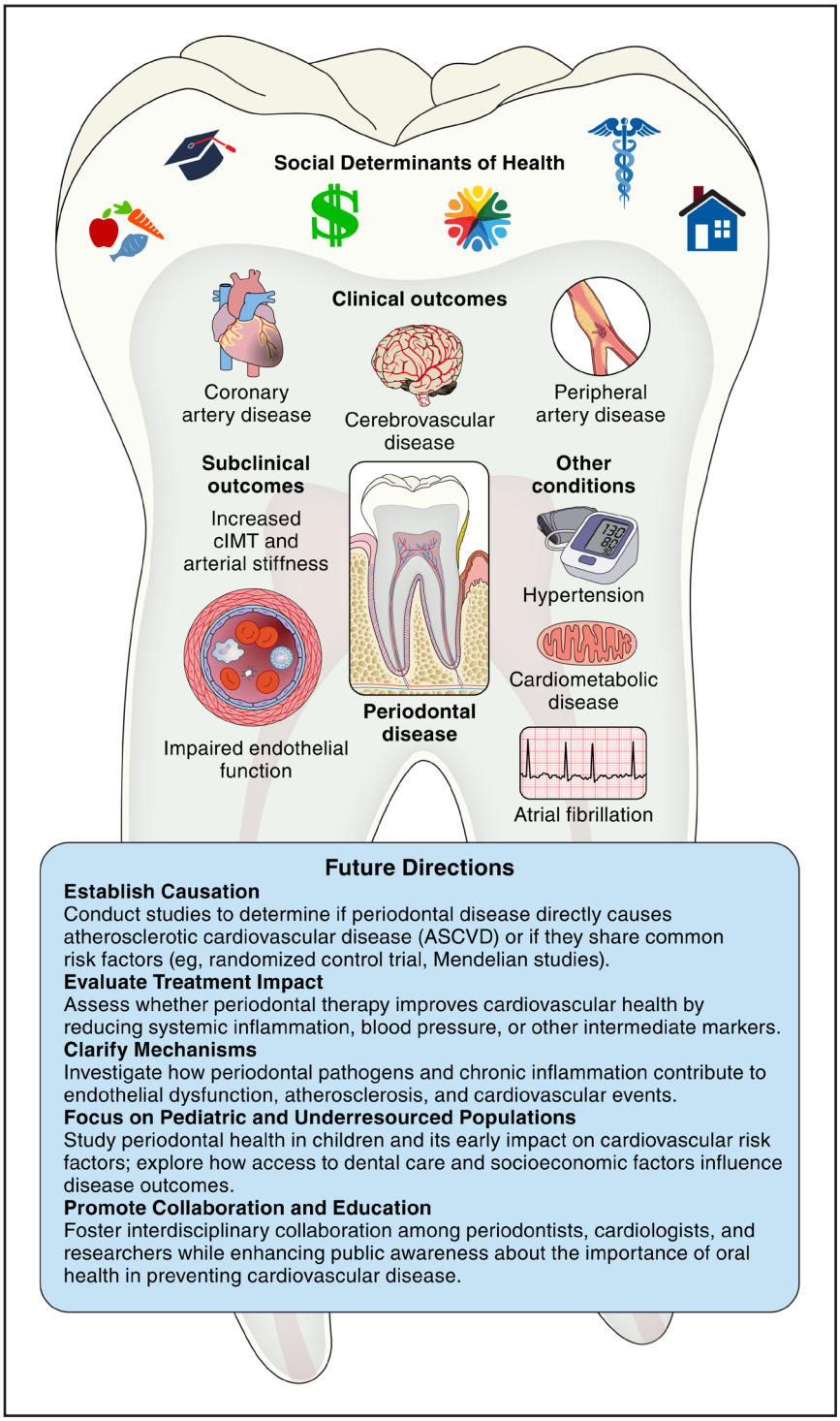


Figure 1. Periodontal disease associations with clinical outcomes, subclinical outcomes, and other conditions.
Social determinants of health, including food insecurity, educational level, economic stability, social and community context, access to health care, and neighborhood and built environment, can affect all of the outcomes listed. Future directions for study are also depicted. CIMT indicates carotid intima–media thickness.

vascular tissues, which may experience acute inflammation, which, in the absence of complete resolution, could lead to chronic inflammation and ASCVD.[17]

Chronic systemic inflammation, antibody cross-reactivity, thrombotic factors, and the oral microbiome comprise indirect association mechanisms.[2] A chronic systemic inflammation component may intensify disease processes.[2,3] Patients with higher circulating levels of the inflammatory marker CRP (C-reactive protein) may have a greater risk of cardiovascular events, including nonfatal MI and death from coronary heart disease.[18,19] Proinflammatory cytokines, such as IL-6 (interleukin-6), IL-18 (interleukin-18), soluble C40 ligand, and TNF (tumor necrosis factor), have also been found to be associated with coronary heart disease.[20] However, a systematic review of recent studies indicated that the adipokines leptin (proinflammatory) and adiponectin (anti-inflammatory), along with their ratio (leptin:adiponectin

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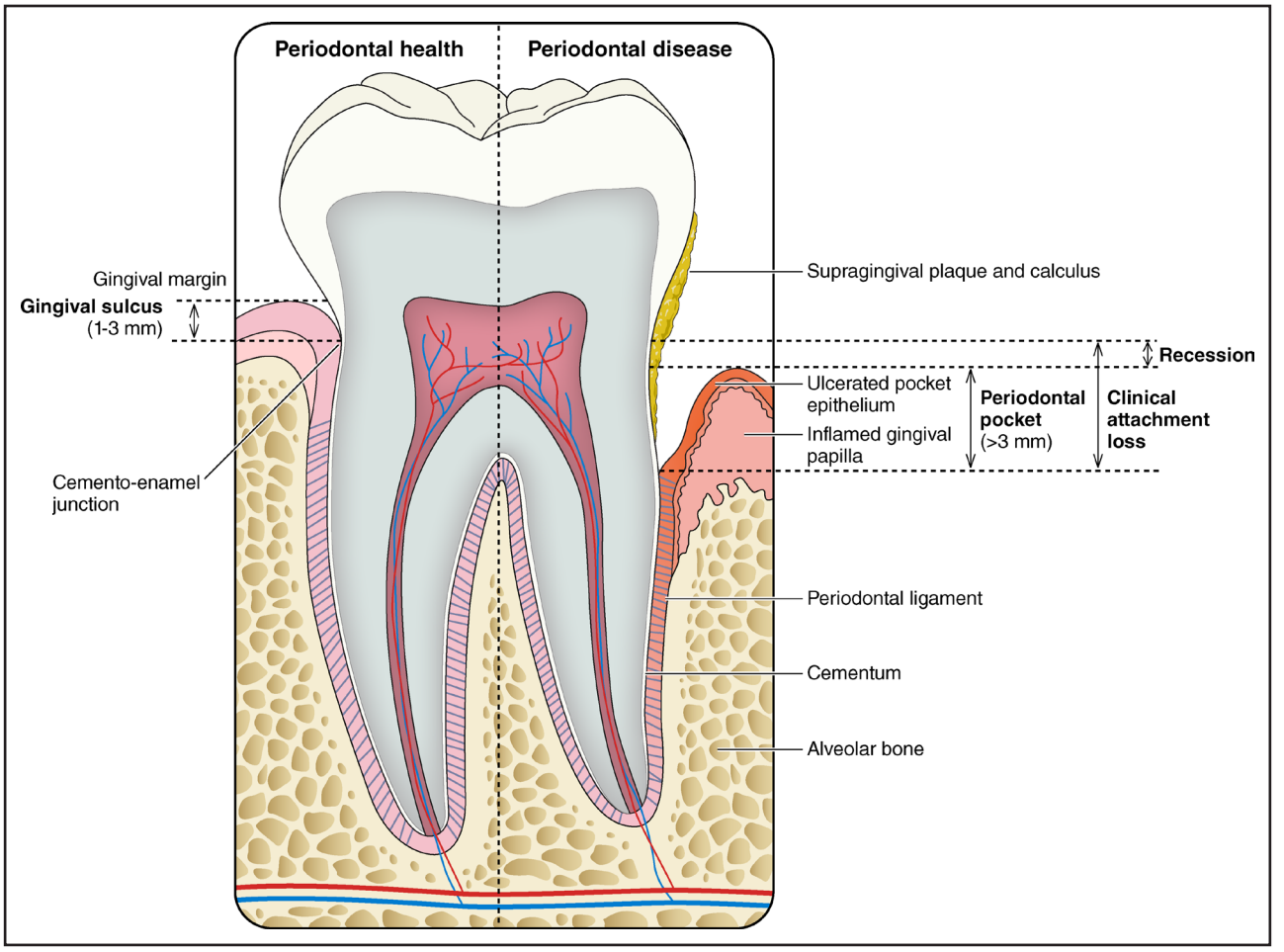


Figure 2. Periodontal anatomy: healthy and diseased state.
The left side of the figure shows healthy periodontal anatomy, with a gingival sulcus of 1 to 3 mm. The right side of the figure depicts periodontal disease, with gingival recession, clinical attachment loss of the gingiva from the tooth, deepened periodontal pocket (>3 mm), ulcerated pocket epithelium, and inflamed gingival papilla, as well as alveolar bone loss.

ratio), may be better indicators of total inflammatory status because of their properties of induction (leptin) and suppression (adiponectin) of more commonly used biomarkers (eg, CRP, TNF, IL-6).[21]

Periodontal disease itself also generates a chronic systemic inflammatory state. Patients with periodontal disease present with higher circulating levels of leptin, CRP, TNF, IL-1 (interleukin-1), IL-6, and IL-8 (interleukin-8),[12,13,22] and decreased adiponectin levels.[11] Further inquiry is needed to elucidate the exact mechanisms by which leptin and adiponectin contribute to periodontal disease and their potential to influence ASCVD.

Cross-reactive autoantibodies against bacterial antigens, particularly those against heat shock proteins, which are produced in response to stress, are also suggested as a possible mechanism by which periodontal infections may promote atherosclerosis.[23–25] The proposed mechanism is through endothelial damage from an immune response to bacterial heat shock proteins. Cross-reactivity between *Porphyromonas gingivalis* and human HSP60 (heat shock protein 60) is capable of promoting atherosclerotic changes due to the subsequent autoimmune response in the vascular endothelium.

Thrombotic factors such as platelet activation and aggregation contribute to another indirect association.[12] Platelets and their activation state are of pivotal importance to the onset and exacerbation of atherosclerosis. Patients with periodontal disease show elevated platelet activation compared with age- and sex-matched controls.

Dysbiosis of the oral microbiome and infection with periodontal pathogens plays a key role in periodontal disease. Bacterial biomarkers of oral dysbiosis have been associated with an increased risk of subclinical atherosclerosis, prevalent and future CAD, and incident and recurrent stroke.[16] Periodontal pathogens, such as the gram-negative bacillus *P gingivalis,* can contribute to inflammatory disease.[26] The detection of periodontal organisms (through DNA, RNA, or antigens) in atheromatous plaque samples and vascular walls may contribute to the progression of atherosclerosis and a procoagulant response.[12]

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Genetic studies have suggested the existence of shared susceptibility genes that are involved in the pathogenesis of ASCVD and periodontal disease.[25] One of the strongest and best replicated genetic cardiovascular disease (CVD) risk loci has been identified on human chromosome 9p21.3. Studies have shown that the 9p21.3 locus is also associated with periodontal disease, suggesting shared susceptibility effects in both ASCVD and periodontal disease. However, there is no confirmation of a causal genetic link between the two.

ASSOCIATION OF PERIODONTAL DISEASE AND ASCVD

Clinical Outcomes

Atherosclerosis

Atherosclerosis of the cerebrovascular, cardiovascular, and peripheral arterial beds is a lifelong process. Systemic inflammation is a known driver of atherosclerotic progression as well as cardiovascular and cerebrovascular events. Proinflammatory conditions associated with clearly established risk include older age, male sex, diabetes, smoking (direct or secondhand), hyperlipidemia, and hypertension, and are the principal targets of primary and secondary prevention.[1,27] Periodontal disease is among many other prevalent drivers of low-grade systemic inflammation, including low levels of physical activity, obesity, disordered sleep, dysbiosis of the bowel or mouth, dietary trans fats and processed food, depression and stress, and exposure to environmental toxins, such as air pollution. Exposure to these often begins in childhood.[28] The combined contribution of these conditions may result in a residual inflammatory risk after more traditionally recognized factors are addressed as part of primary and secondary prevention strategies for atherosclerotic disease.

The additive risk of the proinflammatory state attributable to periodontal disease is difficult to quantify in isolation against the backdrop of other exposures, and controlling for confounding is a well-recognized challenge and quality metric of clinical studies that examine the correlation of periodontal disease and atherosclerosis. In addition, low-grade inflammation due to periodontal disease is associated with powerful known risk factors for CVD, including diabetes, hypertension, smoking, lower socioeconomic status, and a spectrum of less-traditional risk factors. These features may represent unmeasured confounders in studies relating periodontal disease to CVD.

CAD and Acute Coronary Syndromes

CAD and its consequences have been linked to periodontal disease prevalence and severity (Figure 1). In 2013, a systematic review suggested that positive associations between periodontal disease and incident CAD had been identified for specific subgroups, particularly younger adults.[29] The authors did not find evidence of an independent effect of periodontal disease on secondary cardiovascular events. A follow-up review in 2017 suggested that there is robust evidence that periodontal disease independently increased atherosclerotic disease risk when the dominant cardiac risk factors were controlled.[30]

Many studies have shown a strong correlation of periodontal disease with clinical MI events, and systematic reviews and meta-analyses support the association of periodontal disease with CVD, stroke, and cardiac and cerebrovascular death.[31–33] Even more studies have documented subclinical manifestations of atherosclerotic vascular disease. In a study of patients admitted with acute MI, periodontal disease was more prevalent and severe than in age-matched controls after adjustment for smoking, diabetes, and socioeconomic factors.[33] Patients with established atherosclerosis with myocardial ischemia, MI, or stroke merit the full array of secondary prevention treatments, as well as correction of reversible sources of residual risk. The potential benefit of periodontal treatment specifically for secondary prevention of cardiovascular events is discussed further in Effects of Intervention on Periodontal Disease and ASCVD Risk.

Cerebrovascular Disease

Periodontal disease–related inflammation may lead to the occurrence of cerebrovascular events that may be linked to either small vessel or large artery disease. Inflammation of small cerebral blood vessels (arteries, capillaries, and venules) has been mainly related to blood–brain barrier dysfunction, endothelial cell changes, and microglial activation, the pathogenic substratum that accounts for the development of cerebral small vessel disease (CSVD).[34] CSVD is expressed by means of several neuroimaging markers, including white matter hyperintensities of presumed vascular origin, cerebral microbleeds, recent small subcortical infarcts, cortical cerebral microinfarcts, lacunes of presumed vascular origin, enlarged perivascular spaces, cortical superficial siderosis, and brain atrophy.[35] Several meta-analyses have shown that periodontal disease is significantly associated with an increased risk for stroke.[36,37] Furthermore, for individuals with a history of stroke, presence of periodontal disease increases risk for recurrent stroke versus those without periodontal disease.[38] Beyond stroke, periodontal disease is also associated with increased risk of dementia and cognitive impairment.[36]

Regarding the relationship between periodontal disease and lacunes, several studies (but not all) have found a positive association; heterogeneity in study designs and populations may account for inconsistencies.[35,39] Moreover, periodontal disease and CSVD may share risk factors (eg, hypertension, diabetes, smoking), and causality

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has been difficult to assess. The association between periodontal disease and white matter hyperintensities has been less well-studied and results have been inconsistent because of the presence of confounders.[40] Likewise, the association between periodontal disease and cerebral microbleeds is limited. There is no information on the association between periodontal disease and other markers of CSVD.

In addition to CSVD, periodontal disease may result in stenosis or occlusion of major intracranial arteries, which, in turn, can result in the development of large cerebral infarctions or parenchymal brain hemorrhages.[41–43] Involvement of these arteries is often associated with compromise of major extracranial arteries in the neck (in the form of increased carotid intima-media thickness [CIMT] or carotid plaques), giving rise to the term cervicocephalic atherosclerosis. Inasmuch as atherosclerosis is mainly an inflammatory disease, an association with periodontal disease is expected and has been amply demonstrated.[12,13] Whereas biologic plausibility suggests periodontal disease as the exposure and cervicocephalic atherosclerosis as the outcome, heterogeneity in the definition of the exposure as well as a paucity of longitudinal information precludes proper assessment of the direction of this relationship.

Peripheral Artery Disease

Peripheral artery disease affects ≈10% of older adults and is an important marker of atherosclerosis that has been related to an increased risk of coronary disease and stroke. The association between periodontal disease and peripheral artery disease has been confirmed in systematic reviews and meta-analyses.[44,45] However, data are insufficient to determine causality in view of the lack of well-conducted longitudinal studies and because mechanisms underlying peripheral artery disease in the setting of periodontal disease are not fully understood.[46] Release of inflammatory cytokines and the direct effect of pathogens associated with periodontal disease have been suggested as potential causes of this association.

Subclinical CVD Measures

Carotid Intima-Media Thickness

Several observational studies have found that periodontal disease is associated with increased CIMT. Presence of periodontal disease increased the odds of thickened CIMT by 42%, and severe periodontal disease increased the odds by 70% compared with those without periodontal disease.[47] Tsai et al[48] more recently found a dose–response association between each stage of periodontal disease and CIMT, with each increasing stage associated with higher CIMT. These findings are important because increased CIMT is associated with a higher risk for future CVD, and reduction of CIMT progression decreases the relative risk for CVD.[49]

Endothelial Function

In addition to arterial thickening, periodontal disease appears to affect endothelial function, a measure of arterial health that can be an early sign of atherogenesis. Despite differences in study design, a meta-analysis found significantly reduced flow-mediated dilation, a measure of endothelial function, in individuals with periodontal disease compared with controls,[50] suggesting early subclinical vascular changes in patients with periodontal disease.

Arterial Stiffness

Increased large artery stiffness as measured by pulse wave velocity (PWV) is associated with multiple adverse effects on end organs, including myocardial dysfunction, renal disease, and cognitive impairment.[51] When comparing individuals with severe periodontal disease with those with nonsevere periodontal disease, PWV measurements were significantly higher in the severe periodontal disease group.[52] These differences held true even across different PWV measurement techniques, including carotid–femoral PWV, carotid–radial PWV, and brachial–ankle PWV.

Additional Subclinical Outcomes

The arterial differences found in individuals with periodontal disease do not necessarily extend to all vascular modalities. Ultrasound evaluation of carotid artery compliance, elastic modulus, and β stiffness index found no significant association with periodontal disease.[53]

Periodontal Disease and Other Associations

Beyond the association between periodontal disease and acute coronary syndromes mentioned previously, other analyses have identified periodontal disease as a risk factor for atrial fibrillation, heart failure, and chronic kidney disease.[54,55] Furthermore, periodontal disease has been associated with cardiometabolic disease, including dyslipidemia, type 2 diabetes, obesity, and nonalcoholic fatty liver disease.[22,56] An increasing body of evidence also suggests an association between periodontal disease and hypertension even after adjustment for confounders.[57]

Impact of Periodontal Disease in Children

Primordial and primary prevention strategies in children are essential to prevent or reduce inflammatory risk factors, especially given the high prevalence of hypertension, hyperlipidemia, inactivity, and diabetes among young people. Contrasting the number of adult studies on periodontal disease, the number of pediatric studies is limited. In a cohort study done as part of the Cardiovascular Risk in Young Finns Study, the presence of oral infections identified in childhood predicted adult

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subclinical atherosclerosis.[58] Criteria for oral infections included bleeding on probing, periodontal probing depth, caries, and dental fillings. Further study of this same cohort found that childhood caries and oral infections were linked to blood pressure (BP), waist circumference, glucose levels, and metabolic syndrome in adulthood. However, the associations with lipid measures were less pronounced.[59]

Adolescents with periodontal disease were also found to have significantly higher inflammatory markers than those without periodontal disease, and periodontal disease was associated with diastolic BP even after adjustment.[60] In this study, periodontal disease was defined as pathologic periodontal pockets with probing depth ≥4 mm. Other large observational and longitudinal studies in children found that increased frequency of tooth brushing was associated with lower risk of dyslipidemia even after adjustment,[61] and deferred dental care in adolescence and early adulthood was associated with adult adiposity after adjustment for sociodemographic factors.[62] Oral health–based prevention approaches, as well as access to and affordability of dental care for young people, need to be considered in the context of other strategies.

EFFECTS OF INTERVENTION ON PERIODONTAL DISEASE AND ASCVD RISK

In the current scientific statement, we define periodontal nonsurgical intervention as oral hygiene instructions, scaling and root planing (SRP), and antibiotics. To summarize nonsurgical approaches briefly, scaling uses dental instruments, lasers, or ultrasonic devices to remove tartar and related bacteria from tooth surfaces; root planing smooths the root surfaces below the gumline to remove plaque and calculus and allows the gingival tissues to reconnect to the tooth root surface; and topical and oral antibiotics can reduce oral bacteria and concomitant inflammation. The most common interventions to prevent and treat periodontal disease and related local gingival inflammation are nonsurgical and thus are the interventions used in most studies assessing the effect of periodontal disease treatment on ASCVD outcomes.

Surgical interventions include flap/pocket reduction surgery, soft-tissue grafts, bone grafting, guided tissue regeneration, and tissue-stimulating proteins. Surgical interventions are largely unstudied with respect to their effect on ASCVD.

Impact of Periodontal Interventions on ASCVD and Stroke

The Cochrane Oral Health group published systematic literature reviews of studies assessing the effects of periodontal therapy on preventing (primary prevention) or managing (secondary prevention) ASCVD in patients with chronic periodontal disease in 2017,[63] 2019,[64] and 2022.[65] A single pilot study examining secondary prevention, PAVE (Periodontitis and Vascular Events), including 303 participants with periodontal disease, evaluated the effect of SRP versus community care in 5 US centers.[66] The results were inconclusive in supporting or refuting whether SRP can prevent ASCVD recurrence in patients with periodontal disease and was deemed low quality. A randomized clinical trial (RCT) randomized 165 participants with periodontal disease and metabolic syndrome to SRP plus amoxicillin and metronidazole versus supragingival scaling and plaque control in primary prevention of ASCVD events, ASCVD death, and all-cause death. This study was inconclusive; it was underpowered because only 1 death occurred,[67] and it was deemed to have high risk of bias. The Cochrane group called for further research on the topic.

PREMIERS (Periodontal Disease Treatment After Stroke or Transient Ischemic Attack)[68] was a multicenter phase II RCT of 280 patients with stroke or transient ischemic attack and moderately severe periodontal disease randomized to intensive (supra- and subgingival SRP, extraction of hopeless teeth, local antibiotics, oral hygiene instructions, and supportive periodontal disease therapy at 3-month visits for up to 5 sessions) versus standard (supragingival scaling/polishing and site-specific subgingival scaling if probing depth increased >3 mm) periodontal disease treatment. The investigators found the primary outcome over 12 months of death, MI, or recurrent stroke was not statistically different between the 2 groups but trended toward favoring intensive treatment (hazard ratio, 0.65 [95% CI, 0.03–1.38]) with similar rates of adverse events. Secondary outcome measures showed a trend toward improvement in both arms, with significant changes in diastolic BP and high-density lipoprotein levels.

Impact of Periodontal Interventions on Systemic Markers

Individuals with periodontal disease have elevated circulating markers of inflammation known to be associated with ASCVD, raising questions on the potential effect of periodontal disease treatment on systemic markers. The PAVE pilot study assessed systemic high-sensitivity C-reactive protein and found that reduction in high-sensitivity CRP levels at 6 months among those receiving periodontal care was specific to the group with obesity after adjusting for smoking, marital status, and sex.[66] An RCT of patients with metabolic syndrome found that both the SRP and antibiotics and the supragingival scaling and plaque control arms resulted in significant

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reduction in CRP levels after 9 months.[67] In an RCT of 246 participants with angiographically proven coronary heart disease, Bokhari et al[69] found that an intervention of SRP and oral hygiene instructions versus no intervention significantly reduced circulating levels of CRP, fibrinogen, and white blood cells. Moon et al[70] assessed conventional ASCVD risk factors, inflammatory markers, and white blood cells in relation to tooth brushing frequency among 13 761 adults in the Korean National Health and Nutritional Survey (2015–2017) and found that the estimated 10-year ASCVD risk decreased with increasing tooth brushing (13.7% for once daily or less to 7.35% for 3 or more times per day), and, after adjusting for potential confounders, inflammatory markers (high-sensitivity CRP and white blood cells) showed significant reduction by toothbrushing frequency. Studies in children are limited, but Bresolin et al[71] demonstrated improved inflammatory markers (fibrinogen and IL-6) and lipid levels in children after periodontal disease treatment similar to findings in adult studies.

A systematic review and meta-analysis by Teeuw et al[72] showed that periodontal disease treatment reduced ASCVD biomarkers and improved endothelial function particularly in people with ASCVD, diabetes, or both. A subsequent RCT in patients with early-stage periodontal disease found a 3-month advanced periodontal disease self-care regimen versus control had no significant group differences on endothelial function markers, flow-mediated dilation of the brachial artery, or vasodilation-inhibiting serum asymmetric dimethylarginine levels.[73]

Risk factors including BP and glycemic traits have been examined with respect to periodontal disease interventions. A meta-analysis was performed of 8 RCTs with varying comparisons, including periodontal disease treatment versus none and intensive periodontal disease treatment versus supragingival scaling.[74] Overall, no association was seen in systolic or diastolic BP, except in individuals with hypertension, for whom a single study found a decrease in BP at month 2.[75] Supporting this vascular distinction between people with versus without hypertension are meta-analytic reviews finding evidence that periodontal disease treatment may improve flow-mediated dilation, which may be acutely relevant in people with baseline hypertension but progressive toward chronic hypertension in previously normotensive individuals.[50] Regarding glycemic traits, a meta-analysis provided moderate certainty that periodontal disease treatment improves glycemic control in people with diabetes.[76] As for lipids, a meta-analysis of periodontal disease intervention reported improved total cholesterol, triglyceride, and high-density lipoprotein cholesterol levels.[77] Statin therapy for lipid control may also improve the gingival index in periodontal disease, demonstrating a possibly bidirectional relationship between ASCVD risk factors and periodontal disease.[77]

Mendelian Randomization

The effects of periodontal disease are confounded by coincident accumulated shared risk factors with ASCVD. To determine causality, evidence from randomized interventional trials (and meta-analysis of such trials), as well as randomized assortment of genetic variables in the form of Mendelian randomization (MR) analysis can be helpful.

MR is an instrumental variable study design for causal inference. MR leverages the random meiotic assortment of genetic alleles associated with a biologic predictor trait of interest to divide the population into 2 groups. The temporal priority of the random genetic assortment to the outcome negates the possibility of reverse causation between gene and health outcome and creates 2 randomized groups. When the association between gene minor allele and outcome are accounted for by combination of gene to trait and trait to outcome, the gene-driven trait can be causally inferred to be associated with the outcome.

Older data had found that gene variants associated with periodontal disease overlapped as variants associated with coronary heart disease.[78] Recent data used MR to examine the association between genetic proxies of chronic periodontal disease or aggressive periodontal disease on ischemic stroke.[79] In this analysis of ischemic stroke overall, neither large artery atherosclerotic stroke nor small vessel occlusion were associated with genetic instruments, but cardioembolic stroke was associated. Another study examining 5 genetic single nucleotide polymorphisms associated with periodontal disease found no associations with stroke, coronary heart disease, or CIMT.[80]

RESEARCH NEEDS AND FUTURE DIRECTIONS

The observational associations and epidemiologic overlap between periodontal disease and ASCVD suggest a significant connection, but definitive causation and effective intervention strategies remain undetermined (Figure 1). Many studies examining the association between periodontal disease and ASCVD are underpowered and therefore may not find a statistical association although one might be present. Furthermore, current studies may not fully account for upstream causal factors. To elucidate this relationship, well-designed longitudinal studies and RCTs looking at periodontal disease in at-risk populations are needed to investigate the effect of periodontal treatment on systemic inflammatory markers and ASCVD outcomes. Mechanistic studies should focus on further identifying the pathways through which periodontal pathogens and systemic inflammation contribute to atherosclerosis and cardiovascular events. MR studies can help address causality by leveraging genetic variants associated with periodontal disease. Further studies on

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Table. Recent Studies on Periodontitis, Oral Health, and Vascular Outcomes

Study, year	Design	Exposures	Main outcomes	Adjusted variables	Main findings
ASCVD					
Dietrich et al,[29] 2013	Systematic review; 12 studies	Periodontitis	ASCVD	–	All studies except 1 found a positive association between periodontitis and incidence of ASCVD
Dietrich et al,[30] 2017	Systematic review; 22 studies	Periodontitis	ASCVD	–	Chronic periodontitis is independently associated with increased ASCVD risk
Hansen et al,[31] 2016	Cohort; 17 691 cases, 83 003 controls	Periodontitis	ASCVD, mortality	Age, sex, smoking, comorbidities, medication, socio-economic status	IRR, 1.16 (1.04, 1.30) for MI; IRR, 1.51 (1.38, 1.65) for ischemic stroke; IRR, 2.02 (1.87, 2.18) for cardiovascular death
Romandini et al,[32] 2021	Systematic review and meta-analysis; 57 studies	Periodontitis, edentulism	ASCVD, mortality, cancer, pneumonia	–	Periodontitis: RR, 2.58 (2.20, 3.03) for coronary heart disease; RR, 3.11 (2.42, 3.98) for cerebrovascular disease; RR, 1.46 (1.15, 1.85) for all-cause mortality; RR, 1.47 (1.14, 1.90) for cardiovascular mortality; RR, 1.38 (1.24, 1.53) for cancer; RR 0.98 (0.69, 1.38) for pneumonia; edentulism: associated with increased risk for coronary heart disease, cerebrovascular disease, all-cause mortality, cardiovascular mortality, cancer, and pneumonia
Rydén et al,[33] 2016	Case-control; 805 cases, 805 controls	Periodontitis	MI	Smoking status, diabetes, years of education, marital status	OR, 1.28 (1.03, 1.60) after adjustment
Cerebrovascular disease					
Dewan et al,[37] 2024	Systematic review and meta-analysis; 14 studies	Periodontitis, gingivitis	Stroke	–	Pooled effect size, 1.32 (1.04, 1.60) for periodontitis and stroke (all types); pooled effect size, 1.17 (0.42, 1.92) for gingivitis and stroke (all types)
Sen et al,[38] 2013	Cohort; 106 participants	Periodontitis (highest tertile of extent: clinical attachment loss of ≥5 mm)	Recurrent vascular events (stroke, transient ischemic attack, MI, vascular death)	Age, sex, race, hypertension, diabetes, hypercholesterolemia, BMI, coronary artery disease, smoking, excessive alcohol use, education level, annual income	HR, 2.8 (1.2, 6.5) after adjustment for confounders
Leira et al,[39] 2016	Case-control; 62 cases, 60 controls	Periodontitis	Stroke (lacunar infarct)	Model 1: hypertension, smoking, alcohol consumption, statins, chronic periodontitis; model 2: diabetes, alcohol consumption, severe chronic periodontitis	Model 1: OR, 4.20 (1.81, 10.20) for periodontitis and stroke; model 2: OR, 3.53 (1.07, 12.77) for severe periodontitis and stroke
Mayer et al,[40] 2023	Cohort; 2030 participants	CAL, plaque index, DMFT index	WMH and PSMD on brain MRI	Age, sex, education, cardiovascular risk factors	β (CI), 0.000 (−0.002, 0.002) for CAL and WMH; β (CI), 0.001 (−0.001, 0.003) for plaque index and WMH; β (CI), 0.008 (−0.002, 0.018) for DMFT and WMH; β (CI), 0.004 (−0.004, 0.012) for CAL and PSMD; β (CI), 0.010 (0.003, 0.016) for plaque index and PSMD; β (CI), 0.046 (0.011, 0.081) for DMFT and PSMD
Sen et al,[43] 2024	Cohort; 6155 participants	Periodontitis, caries	ICAS	Age, sex, race, hypertension, diabetes, dyslipidemia, education level, smoking status, alcohol use, time between visits 4 and 5 (y)	OR, 2.59 (1.16, 5.76) for PPC V and ≥50% ICAS; OR, 1.94 (1.02, 3.71) for PPC IV and <50% ICAS; OR, 1.80 (1.04, 3.11) for PPC VII and <50% ICAS
Peripheral artery disease					
Wang et al,[44] 2019	Systematic review and meta-analysis; 25 studies	Periodontitis	PAD	–	OR, 1.60 (1.41, 1.82)
Yang et al,[45] 2018	Systematic review and meta-analysis; 7 studies	Periodontitis	PAD	–	RR, 1.70 (1.25, 2.29) periodontitis between participants with vs those without PAD

(*Continued*)

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Table. Continued

Study, year	Design	Exposures	Main outcomes	Adjusted variables	Main findings
Arsiwala et al,[46] 2022	Cohort; 9793 participants	Periodontitis (self-reported and clinical); tooth loss (self-reported); history of periodontal disease treatment (self-reported)	PAD	Age, sex, race, education level, diabetes, pack-years of smoking, systolic blood pressure, antihypertensive medication, total cholesterol, HDL-C, lipid-lowering therapy, history of CVD	HR, 1.54 (1.20, 1.98) for tooth loss and PAD; HR, 1.37 (1.05, 1.80) for history of periodontal disease treatment and PAD; HR, 1.38 (1.09, 1.74) for periodontitis (self-reported) and PAD; HR, 1.53 (0.94, 2.50) for severe periodontitis (clinical) and PAD
Subclinical CVD measures					
Ding et al,[47] 2022	Meta-analysis; 7 studies	Periodontitis	CIMT	–	OR 1.42 (1.16, 1.75) for periodontitis and increased CIMT; OR, 1.70 (1.24, 2.33) for severe periodontitis and increased CIMT
Tsai et al,[48] 2023	Cross-sectional; 486 participants	Periodontitis	CIMT	Age, sex, tooth brushing frequency, alcohol intake, tobacco smoking, BMI	OR, 1.41 (0.60, 3.29) for stage I periodontitis and increased CIMT; OR, 1.62 (0.79, 3.31) for stage II periodontitis and increased CIMT; OR, 3.20 (1.42, 7.18) for stage III periodontitis and increased CIMT
Orlandi et al,[50] 2014	Systematic review and meta-analysis; 22 studies	Periodontitis	CIMT, FMD	–	Mean increase of 0.08 mm (95% CI, 0.07, 0.09) in CIMT; mean decrease of 5.1% (95% CI, −8.11, −2.08) in FMD
Darnaud et al,[52] 2021	Systematic review and meta-analysis; 10 studies	Severe periodontitis	cfPWV, crPWV, baPWV	–	Mean increase of 0.84 m/s (95% CI, 0.50, 1.18) in cfPWV; mean increase of 0.34 m/s (95% CI, 0.14, 0.54) in crPWV; mean increase of 0.48 (95% CI, 0.15, 0.82) in baPWV
Ollikainen et al,[53] 2022	Cross-sectional; data set 1, n=157; data set 2, n=536	No. of teeth with periodontal pockets ≥4 mm; no. of sextants with periodontal bleeding	Measures of common carotid artery: compliance, Peterson elastic modulus, Young elastic modulus, β stiffness index	Age, sex, educational level, serum lipid composition, BMI, level of physical activity, alcohol consumption, systolic blood pressure	Data set 1 adjusted β estimates (95% CI); no. teeth with periodontal pockets, 15.80 (−3.99, 35.58) for Peterson elastic modulus; 61.02 (−37.90, 159.95) for Young elastic modulus; no. sextants with periodontal bleeding, 31.06 (−13.33, 75.45) for Peterson elastic modulus; 121.16 (−100.63, 342.96) for Young elastic modulus; findings were not significant for compliance or β stiffness index; findings in data set 2 were also not significant
Pediatric studies					
Pussinen et al,[58] 2019	Cohort study; 755 participants	Signs of childhood oral infection: bleeding on probing, periodontal probing depth, caries, dental fillings	Adult CIMT	Age, sex, BMI, systolic and diastolic blood pressure, plasma HDL-C, LDL-C, triglycerides, glucose level, smoking status, family income	RR, 1.87 (1.25, 2.79) for any sign of oral infection and association with increased CIMT; RR, 1.95 (1.28, 3.00) for presence of all 4 signs of oral infection and association with increased CIMT
Pussinen et al,[59] 2020	Cohort study; 755 participants	Signs of childhood oral infection: bleeding on probing, periodontal probing depth, caries, dental fillings	Adult metabolic syndrome	Age, sex, childhood BMI, childhood family income, adulthood smoking status, socioeconomic status, interaction terms between caries and periodontal measures	RR, 1.25 (0.90, 2.45) for childhood caries and adult metabolic syndrome; RR, 1.27 (1.02, 1.99) for childhood fillings and adult metabolic syndrome
Zeigler et al,[60] 2015	Cross-sectional; 75 participants	Periodontal pocket depth ≥4 mm	Blood pressure	BMI SDS, age, sex, mother's country of birth, bleeding on probing >25%, leptin, MCP-1, TSH, IL-6, IL-8, cholesterol	Adjusted β estimate (95% CI), 0.48 (2.68, 15.67) for periodontal pocket depth ≥4 mm and diastolic blood pressure; no significant association between periodontal pocket depth and systolic blood pressure

All studies were conducted in adults except those indicated as pediatric studies. ASCVD indicates atherosclerotic cardiovascular disease; baPWV, brachial–ankle pulse wave velocity; BMI, body mass index; CAL, clinical attachment loss; cfPWV, carotid–femoral pulse wave velocity; CIMT, carotid intima-media thickness; crPWV, carotid–radial pulse wave velocity; CVD, cardiovascular disease; DMFT, decayed/missing/filled teeth index; FMD, flow-mediated dilation; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; ICAS, intracranial atherosclerosis; IL-6, interleukin-6; IL-8, interleukin-8; IRR, incidence rate ratio; LDL-C, low-density lipoprotein cholesterol; MCP-1, macrophage chemoattractant protein-1; OR, odds ratio; PAD, peripheral artery disease; PPC, periodontal profile class; PSMD, peak width of skeletonized mean diffusivity; RR, risk ratio (relative risk); SDS, standard deviation score; TSH, thyroid stimulating hormone; and WMH, white matter hyperintensity.

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subclinical cardiovascular measures, such as CIMT, endothelial function, and arterial stiffness, are essential for identifying at-risk individuals and understanding disease progression. In addition, the role of socioeconomic status, access to dental care, and other social determinants in the prevalence and outcomes of periodontal disease and ASCVD should be explored to develop targeted prevention and treatment strategies. Pediatric populations require focused research on the effect of precursors of periodontal disease, such as gingivitis and related inflammatory markers, on cardiovascular risk factors, emphasizing early prevention and intervention. The identification of novel biomarkers and the use of advanced imaging techniques can enhance understanding of the periodontal disease–ASCVD link. Interdisciplinary collaboration among cardiologists, periodontists, epidemiologists, geneticists, radiologists, and other health care professionals is essential for developing integrated care models addressing both oral and cardiovascular health. Evaluating the effectiveness of patient education and public health initiatives in reducing the burden of periodontal disease and its potential effect on cardiovascular health is crucial.

SUMMARY

ASCVD continues to be the leading cause of death in the United States and worldwide. This scientific statement advances our understanding by emphasizing the growing evidence supporting an association between periodontal disease and CVD and sheds light on potential mechanisms to explain the association (Table). Current studies do not clearly show causation, and the effect of periodontal disease treatment on CVD events is inconclusive. However, there is strong evidence that treating periodontal disease improves intermediate outcome measures, such as BP, high-density lipoprotein cholesterol level, and inflammatory markers. This is an important finding because these outcome measures are known to increase future cardiovascular risk and provide a possible link between periodontal disease and ASCVD. To further clarify the mechanistic link between periodontal disease and ASCVD, more pediatric studies are needed, along with longitudinal studies from childhood into adulthood. Additional studies examining the effect of periodontal disease treatment on both intermediate outcomes and CVD events are also needed. MR techniques may provide further clarity on the link between periodontal disease and ASCVD. Although there is evidence for an association between periodontal disease and CVD, evidence for a cause-and-effect relationship is elusive. More stringently controlled intervention studies are needed to determine the long-term effect of periodontal intervention on ASCVD progression and outcomes.

CLINICAL RELEVANCE

Although periodontal disease clearly contributes to the chronic inflammation that has been associated with CVD, there is no direct evidence of causality or that periodontal therapy will help prevent CVD. However, all therapies that lessen the lifetime exposure to inflammation appear to be beneficial. Therefore, the treatment and control of periodontal disease and associated inflammation may contribute to the prevention and control of CVD. Periodontal disease is more common in individuals with poor oral hygiene and other CVD risk factors (eg, diabetes, hypertension, obesity, smoking). High-risk individuals with CVD risk factors may particularly benefit from regular dental screenings and targeted periodontal care to mitigate systemic inflammation. Referral to a dental specialist, such as a periodontist, is especially important for these individuals to ensure comprehensive management of oral and systemic health.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Disclosures

Writing Group Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives ≥$5000 during any 12-month period, or ≥5% of the person's gross income; or (b) the person owns ≥5% of the voting stock or share of the entity, or owns ≥$5000 of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

†Significant.

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Reviewer Disclosures

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