An umbrella review of systematic reviews of the evidence of a causal relationship between periodontal disease and cardiovascular diseases: Position paper from the Canadian Dental Hygienists Association

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ABSTRACT

Previous position papers have confirmed associations between periodontal disease and cardiovascular disease. Causal associations have not been confirmed and have been the source of much confusion for oral health professionals and the public. **Aim:** To investigate whether sufficient evidence exists for a causal relationship between periodontal disease and cardiovascular disease. **Methods:** The PICO question was "For adults in good general health who are diagnosed with periodontal disease, will receiving non-surgical periodontal therapy (NSPT), as compared to not receiving NSPT, lower their risk for cardiovascular diseases?" Only systematic reviews (SRs) with or without meta-analyses (MAs) of randomized controlled trials published in the English language between 2007 and 2019 were included. Databases searched included PubMed, MEDLINE, EbscoHost, CINAHL, Scopus, Cochrane Registry of Systematic Reviews, and Clinical Trials Registry. Quality assessments were conducted by both authors using the PRISMA checklist. The Bradford Hill criteria were used to determine evidence for causality. **Results:** Of 53 cardiovascular disease studies retrieved, 7 met the inclusion criteria, of which 6 contained MAs. Results were mixed for various periodontal interventions lowering the risk for cardiovascular outcomes. Only one SR used cardiovascular events as a direct outcome; the other 6 used various surrogate measures. **Conclusions:** Bradford Hill criteria analysis failed to support a causal relationship between periodontal disease and cardiovascular disease.

RÉSUMÉ

Les énoncés de position précédents ont confirmé des liens entre la maladie parodontale et les maladies cardiovasculaires. Des associations causales n'ont pas été confirmées et ont été la source de beaucoup de confusion pour les professionnels de la santé buccodentaire et la population. **But :** Étudier s'il y a suffisamment de preuves qu'un lien de causalité existe entre la maladie parodontale et les maladies cardiovasculaires. **Méthodologie :** La question PICO était : « Les adultes en bonne santé générale, qui ont reçu un diagnostic de parodontite, auront-ils une réduction de leur risque de maladies cardiovasculaires s'ils reçoivent une thérapie parodontale non chirurgicale (TPNC), en comparaison à ne pas recevoir de thérapie parodontale non chirurgicale? » Seules les revues systématiques (RS) avec ou sans méta-analyse (MA) d'essais comparatifs randomisés publiés en anglais entre 2007 et 2019 ont été incluses. Les recherches de bases de données ont été effectuées, entre autres, dans PubMed, MEDLINE, EbscoHost, CINAHL, Scopus, le registre de revues systématiques Cochrane et le registre d'essais cliniques. Des évaluations de la qualité ont été menées par les 2 auteurs à l'aide de la liste de vérification PRISMA. Les critères de Bradford Hill ont été utilisés pour déterminer la preuve de causalité. **Résultats :** Dans les 53 études repérées sur la maladie cardiovasculaire, 7 répondaient aux critères d'inclusion, et parmi celles-ci, 6 comprenaient des MA. Les résultats en matière de diminution du risque d'effets cardiovasculaires étaient mixtes selon les différentes interventions parodontales effectuées. Une seule RS a utilisé les effets cardiovasculaires comme résultat direct, les 6 autres ont employé diverses mesures de remplacement. **Conclusions :** L'analyse de critère de Bradford Hill n'a pas réussi à appuyer un lien de causalité entre la maladie parodontale et les maladies cardiovasculaires.

Keywords: cardiovascular diseases, meta-analysis, oral health, periodontal disease, periodontal treatment, periodontitis, stroke, systematic reviews
CDHA Research Agenda categories: risk assessment and management; capacity building of the profession

CANADIAN DENTAL HYGIENISTS ASSOCIATION POSITION STATEMENT

The Canadian Dental Hygienists Association acknowledges that, although associations between periodontal disease and cardiovascular disease have been well established, there is insufficient evidence that periodontal disease causes cardiovascular disease.

INTRODUCTION

Relationships between periodontal disease and a number of systemic diseases have been proposed since the late 1800s when physicians speculated that bacteria from the mouth caused everything from brain abscesses to arthritis.[1,2] With the onset of "periodontal medicine" in the early 1990s, studies investigating the relationships between numerous oral and systemic conditions have increased, with inflammation now recognized as a common factor.

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Despite the amount of research published over the last 30 years, questions remain about the exact nature of these relationships. While relationships may be in the form of associations or correlations, they should not be assumed as causal.

Unfortunately, the differences between assumptions and causality are not well understood and the terms are often used interchangeably. A relationship merely describes how 2 variables *might* somehow be related or connected to each other. For instance, lung cancer rates are higher for people without a postsecondary education (who tend to smoke more), but that does not mean that someone can reduce his or her cancer risk just by getting a college or university education.[3] An "association" refers to "a relationship between an exposure (or a characteristic) and a disease that is statistically dependent; that is, the presence of one alters the probability of observing the presence of the other. An association is a necessary condition of a causal relationship, but not all associations are causal. If there is no association, the variables are said to be independent."[4]

A correlation is a relationship in which there is a "Linear association between two continuous or ordinal variables. The measure of the correlation is the correlation coefficient, which ranges from 1 (perfect positive association, e.g., as one variable increases, the second one also increases at the same rate) through 0 (no association) to a −1 (perfect negative association, e.g., as one variable increases, the second one decreases at the same rate)."[4]

In order for a relationship to be coined as "causal," actual "cause and effect" must be determined through a very rigorous set of criteria. One must be able to state with certainty that "A" causes "B" (a specific exposure has been shown to cause a specific outcome).[4] Randomized clinical trials (RCTs) provide the strongest evidence of cause and effect, rather than the outcome happening by chance. These experimental studies are the most methodologically challenging and ones in which the researcher controls or manipulates the variables (i.e., the intervention, its timing and dose) under investigation, such as in testing the effectiveness of a treatment, as compared to another treatment or a placebo.[5]

Often, when clinicians read a research article that is reporting a correlation or an association between an oral disease and a particular outcome of interest, they automatically, and incorrectly, jump to the conclusion that the relationship is causal. Prime examples of such misinterpretations are the assumption that periodontitis is one cause of heart disease or of adverse pregnancy outcomes, or that stress causes periodontitis. It is important for clinicians to understand that correlations and associations do not imply or equal causality. In fact, incorrect assumptions of causality are a major public

Table 1. The Bradford Hill criteria for causality[6]

Criteria	Meaning
Strength of association	A strong association is more likely to have a causal component than is a modest association. Strength of the association is determined by the types of existing studies. The highest-level studies from the evidence pyramid would represent the strongest associations (i.e., RCTs and systematic reviews with meta-analyses). Results from these studies must demonstrate an odds ratio or relative risk of at least 2.0 or above in order to be meaningful. Anything between 1 and 2 is weak while >2 is moderate and >4 is considered strong.
Consistency	A relationship is repeatedly observed in all available studies.
Specificity	A factor influences specifically a particular outcome or population. The more specific an association between a factor and an effect, the greater the probability that it is causal.
Temporality	The cause must precede the outcome it is assumed to affect (e.g., smoking before the appearance of lung cancer). Outcome measured over time (longitudinal study).
Biological gradient (dose-response)	The outcome increases monotonically with increasing dose of exposure or according to a function predicted by a substantive theory (e.g., the more cigarettes one smokes, the greater the chance of the cancer occurring).
Plausibility	The observed association can be plausibly explained by substantive matter (i.e., biologically possible).
Coherence	A causal conclusion should not fundamentally contradict present substantive knowledge. (Studies must not contradict each other.)
Experiment	Causation is more likely if evidence is based on randomized experiments or a systematic review of randomized experiments. However, these RCTs may not be ethically possible and thus prospective rather than experimental studies, such as cohort studies, may be the highest level of evidence available.
Analogy	For analogous exposures & outcomes an effect has already been shown (e.g., Effects first demonstrated on animals or an effect previously occurring on humans such as the effects of thalidomide on a fetus during pregnancy).

Source: Lavigne SE. From Evidence to Causality: How Do We Determine Causality? [Online course]. 2018. Available from: https://www.dentalcare.com/en-us/professional-education/ce-courses/ce530

health concern. From a public health perspective, no evidence should be considered causal unless it has gone through very rigorous scrutiny using standard public health guidelines such as the Bradford Hill criteria for causality[6] (Table 1).

In 2004, Lux and Lavigne[7,8] published a position paper for the Canadian Dental Hygienists Association (CDHA) in 2 parts, outlining the nature of the proposed linkages between periodontal disease and 4 systemic conditions: cardiovascular diseases, preterm low birth weight babies, respiratory diseases, and diabetes. Updates to those first position papers were published in the *Canadian Journal of Dental Hygiene* in November/December 2006[9] and January/February 2007,[10] in which the author reported associations between periodontal disease and cardiovascular diseases, diabetes, adverse pregnancy outcomes, and respiratory diseases (in particular, pneumonia in health-compromised seniors).

A recent systematic mapping of registers of clinical research trials conducted on periodontal medicine revealed 57 conditions that are currently hypothesized to be linked with periodontal diseases.[11] While it is beyond the scope of this current position paper to explore all of these proposed linkages, the status of 10 of these hypotheses will be evaluated in a series of position papers written by the same authors and released in the coming months by CDHA. These forthcoming position papers will assess the nature of the relationships between periodontal disease and diabetes, obesity, respiratory diseases, rheumatoid arthritis, Alzheimer disease, end-stage renal disease, inflammatory cancers and influenza.

The purpose of these updated position papers is to review the research undertaken since the publication of the last CDHA position papers in 2006 and early 2007 on these proposed relationships. Unlike the methodology used for the previous position papers and updates, this investigation is more specific in looking at whether the state of the evidence has evolved from one of associations to one of actual causality. Determining a causal relationship requires studies that have examined an intervention, thus only the highest levels of evidence will be sought for this update. This specific position paper investigates whether a causal relationship exists between periodontal disease and cardiovascular diseases.

METHODOLOGY

The overarching PICO question developed for the first 5 oral–systemic connections to be explored in this series of position papers was customized in this paper for cardiovascular diseases. "For adults in good general health who are diagnosed with periodontal disease (**Population**), will receiving non-surgical periodontal therapy (NSPT) (**Intervention**), as compared to not receiving NSPT (**Comparison group**), lower their risk for cardiovascular diseases? (**Outcome**)"

Eligibility criteria

Both authors independently searched the literature, limiting the search to systematic reviews (SRs) with or without meta-analyses (MAs) of intervention studies using the inclusion and exclusion criteria presented in Table 2. SRs and MAs of observational studies were excluded.

Search strategy

a. Databases searched included PubMed, MEDLINE, EbscoHost, CINAHL, Scopus, Cochrane Registry of Systematic Reviews, and Clinical Trials Registry (clinicaltrials.gov). Additionally, bibliographies of retrieved articles were searched for further relevant systematic reviews and meta-analyses and added when appropriate.
b. Keywords used for each search were as follows: cardiovascular diseases; stroke; periodontal disease; periodontitis; periodontal treatment; oral health; AND systematic reviews; meta-analysis
c. Search strategies (limited to publications after 2007 and in the English language):
    - cardiovascular disease and periodontal disease and systematic reviews
    - stroke and periodontal disease and periodontal treatment and systematic reviews
    - cardiovascular disease and oral health and systematic reviews
    - stroke and oral health and systematic reviews

Table 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Published between 2007 and 2019	Published before 2007
English language	Languages other than English
Systematic reviews with or without meta-analyses (MAs) of RCTs (or cohort studies if no SRs of RCTs were available)	Abstracts, posters, conference proceedings, editorials or commentaries, duplicate studies, narrative reviews, RCTs, observational studies/both cohort and case–control and systematic reviews of observational studies and/or case–control studies.
Studies involving humans	Animal studies (in vivo, ex vivo) and in vitro studies

Study selection

Both authors independently screened the titles and abstracts of all articles retrieved by the search using the inclusion criteria and then discussed their choices to reach consensus regarding their suitability for full-text reading. Both authors independently reviewed the selected full-text articles and reached consensus on their inclusion or exclusion.

Quality assessment

The methodological quality of the selected systematic reviews and meta-analyses was assessed blindly by both authors using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist tool.[12] Scores were then compared and discussed where inconsistencies occurred to reach consensus.

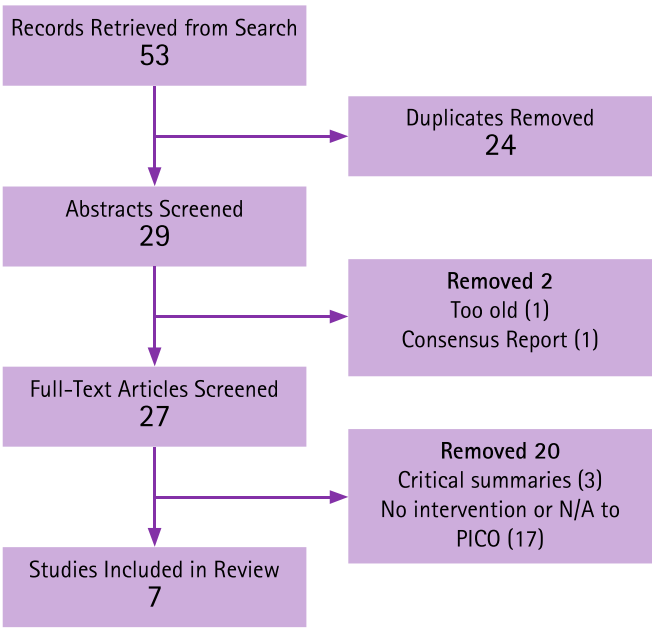
Data extracted

The following information was extracted from each selected SR or MA and compiled in table format: year published, number of RCTs included, country of origin, methods used for assessing risk of bias, heterogeneity, outcomes measured, and conclusions of the findings.

RESULTS

A total of 53 reviews were retrieved from database searches and articles identified within these reviews. After eliminating duplicates and articles that did not meet the inclusion criteria, the authors retained 7 studies[13-19] that were eligible for review. A flow diagram (Figure 1) illustrates the details of the selection process; Table 3 reports the reasons for elimination of full-text articles that did not meet the inclusion criteria. One exception was the inclusion of a 2006 SR/MA[19] because it contained studies that were not included in the previous 2006 CDHA position paper.

Figure 1. Cardiovascular search flow diagram



Results of the quality appraisal of the 7 included systematic reviews and meta-analyses are shown in Table 4. Based on the 27 PRISMA checklist items, scores ranged from 15 to 25. Agreement between the 2 independent evaluators was close to 100%, with scores being off by only 1 to 2 points. The quality of the studies was generally moderate to high, however 3 studies did not report risk of bias[17–19] and one study did not include a quality assessment tool.[17]

Outcomes of the 7 SRs/MAs of intervention studies showed mixed results for a variety of periodontal treatments lowering the risk for cardiovascular outcomes. Only one study[20] included within one SR[13] directly used cardiovascular events as outcomes; the remainder used various surrogate measures including endothelial function, arterial stiffness, hsCRP, TNF-a, Fibrinogen, IL-6, total cholesterol, and HDL-Cholesterol. Three (3) studies[13,14,19] showed no relationship between periodontal treatment and cardiovascular risk while two (2) studies[15,16] reported positive outcomes for improving endothelial function[15] and several biomarkers of CVD.[16] Two studies (2)[17,18] reported mixed results. These results are illustrated in Table 5.

DISCUSSION

A misunderstanding has existed for several years regarding the relationship between periodontal disease and cardiovascular disease. In 2012, this misunderstanding came to the attention of the public through a press release by the American Academy of Periodontology (AAP) stating "Periodontal Disease Linked to Cardiovascular Disease."[21] This statement was based on the results of a 2012 systematic review published in the American Heart Association's journal *Circulation*.[22] Its findings were twofold: 1) "observational studies support an association between periodontal disease and atherosclerotic heart disease independent of known confounders" and 2) "they do not, however, support a causative relationship."[22] Unfortunately, this initial press release failed to include the second finding, but other news outlets quickly noted this discrepancy and released another contradictory statement "No Proof that Gum Disease Causes Heart Disease."[23] Although the American Heart Association attempted to clarify the controversy, it created confusion both within the oral health professions and among the public.

The purpose of this umbrella review was to examine the second part of this controversy, specifically to determine if sufficient evidence exists demonstrating that NSPT lowers the risk for cardiovascular events, thus bringing us closer to determining a causal relationship. Given the multifactorial nature of cardiovascular disease, and by not using direct cardiovascular (CV) outcomes following periodontal therapy, there is insufficient evidence to satisfy the Bradford Hill criteria of temporality and experiment. When surrogate measures are used, one can only make assumptions that NSPT may assist in lowering the risk of a cardiovascular event. RCTs examining direct CV outcomes

Table 3. Cardiovascular screened articles included and deleted

	Included	Deleted	Reason for deletion
1.	Li et al.[13] **2017** (Cochrane) (1 RCT)	Lockhart et al.[22] 2012 (US)	N/A to PICO
2.	Schmitt et al.[14] **2015** (France) (8 observational & 2 intervention studies)	Martin-Cabezas et al.[28] 2016 (France)	No intervention studies & only 2 cohort studies out of 20 studies
3.	Orlandi et al.[15] **2014** (UK) (25 cohort & 1 intervention study)	Dai et al.[29] 2015 (China)	Not relevant to PICO
4.	Teeuw et al.[16] **2014** (Netherlands) (25 intervention studies)	Xian-Tao Zeng et al.[30] 2016 (China)	No intervention studies included
5.	Teixeira de Freitas et al.[17] **2012** (Brazil) (4 RCTs & 7 non-RCT intervention trials)	Lopez N.[31] 2014 (Chile)	Critical summary of Teeuw et al.
6.	Paraskevas et al.[18] **2008** (Netherlands) (4 intervention studies)	Levac et al.[32] 2010 (Canada)	N/A to PICO (scoping review)
7.	Ioannidou et al.[19] **2006** (US) (7 cohort and 3 RCTs)	Cheng et al.[33] 2018 (China)	No intervention studies
8.		Leira et al.[34] 2017 (Spain)	No intervention studies
9.		Sfyroeras et al.[35] 2012 (Greece)	No intervention studies
10.		Kelly et al.[36] 2013 (US)	N/A to PICO
11.		Mustapha et al.[37] 2007 (US)	N/A to PICO
12.		Shi et al.[38] 2016 (China)	No intervention studies
13.		Lam et al.[39] 2011 (UK)	N/A to PICO
14.		Matthews D.[40] 2011 (Canada)	Critical summary of Lam et al.
15.		Dietrich et al.[41] 2013 (UK)	N/A to PICO
16.		Xu et al.[42] 2017 (China)	N/A to PICO
17.		Leng et al.[43] 2015 (China)	N/A to PICO
18.		Merchant A.[44] 2012 (US)	Critical summary of Lockhart et al.
19.		Lafon et al.[45] 2014 (France)	N/A to PICO
20.		Helfand et al.[46] 2009 (US)	N/A to PICO

as an endpoint are difficult to conduct and, in most instances, considered unethical.

The sole SR that used a direct CV outcome was conducted as a Cochrane review by Li and colleagues.[13] Their inclusion criteria sought out RCTs and/or quasi-RCTs that included patients diagnosed with periodontal disease who had either previous cardiovascular disease (secondary prevention study) or no cardiovascular disease (primary prevention study) and in which patients in the intervention group received active periodontal therapy compared to maintenance therapy, no periodontal treatment or another kind of periodontal treatment in the control group. No primary prevention studies focused on the prevention of cardiovascular disease were identified, and only one secondary prevention study was located.[20] This study compared the effects of NSPT with community care on patients previously identified as having either ≥50% blockage of one coronary artery or a coronary event within 3 years of the study, with a follow-up period of 6 months to 25 months. Although the study measured adverse CV events, the authors did not report any data on deaths. No statistically significant differences between the 2 groups were found. Authors of the SR found the included study to be at high risk of bias due to protocol deviation and lack of follow-up. The study was classified as being of very low quality, providing insufficient evidence to either support or refute whether NSPT could prevent the recurrence of CV events.[13]

The remaining 6 SRs investigated the effects of NSPT on several surrogate measures with mixed results. One SR by Schmitt et al.[14] studied the effects of NSPT on arterial stiffness, considered a marker of atherosclerosis and a risk factor for cardiovascular disease. Of the 10 studies included in their review, 2 were intervention studies and only 1 of the 2 was an RCT. Given the difference in study design, no meta-analysis was conducted comparing these 2 studies,

Table 4. Quality appraisal and summary of the systematic reviews/meta-analyses (n = 7)

Author (Country)	PRISMA score	Heterogeneity	Risk of bias	Quality assessment instrument	Comments	Included meta-analysis of the SR
Li et al.[13] **2017** Cochrane Review (UK)	25/27	N/A (only one study)	High (Due to protocol deviation and lack of follow-up)	Cochrane Handbook for Systematic Reviews of Interventions Very low-quality evidence found	1 RCT (303 participants) Results: RR 0.72 Measured effects of Periodontal treatment directly on prevention of CV events	N/A Not possible as only 1 study included
Schmitt et al.[14] **2015** (France)	20/27	Moderate to high	Only 1 RCT included in quantitative analysis and it had a low risk of bias	Cochrane Handbook for Systematic Reviews of Interventions used for RCTs Newcastle-Ottawa Scale used for non-RCTs	10 studies included Only 2 intervention studies showed contradictory results on PT reducing arterial stiffness Measured effectiveness of periodontal treatment on reducing arterial stiffness	Yes Studies included in meta-analysis: 7 observational and 1 RCT but no MA performed with just the 2 intervention studies.
Orlandi et al.[15] **2014** (UK)	23/27	High	Possible selection bias noted	Newcastle-Ottawa Scale for non-RCTs	Measured effects of periodontal treatment on endothelial function 35 studies included in qualitative analysis 22 studies included in quantitative synthesis (3 of 6 RCTs used in MA) MA resulted in statistically significant improvement in endothelial function following periodontal therapy	Yes (included 22 studies) Three were RCTs and used separately to assess the effects of periodontal treatment on endothelial function through flow-mediated dilation.
Teeuw et al.[16] **2014** (Netherlands)	22/27	High	Publication or other bias noted in MA.	Van der Weijden et al (2009)	7 trials included periodontitis patients in good systemic health; 18 trials included periodontitis patients with comorbidities A variety of surrogate outcomes measured. (hsCRP; IL-6; TNF-a; Fibrinogen; triglycerides; total cholesterol; HDL; and LDL; HbA1c and blood pressure). Concluded that periodontal therapy improves surrogate markers for CVD but more so in those with existing co-morbidities	Yes (included all 25 trials)
Teixeira de Freitas et al.[17] **2012** (Brazil)	20/27	Low	Not reported	None used	4 RCTs Concluded that all 4 studies reduced CRP post NSPT, but only 2 were statistically significant. Measured effectiveness of periodontal treatment on reduction of CRP	Yes 4 RCTs used
Paraskevas et al.[18] **2008** (Netherlands)	18/27	Low	Indicated it was explored but none reported or discussed.	Cochrane Handbook of Systematic Reviews	4 Tx studies (Total treated 152; total controls 134) Although hsCRP reduced in intensive treatment groups. No statistically significant differences between standard & intensive treatment were found Measured effects of periodontal therapy on hsCRP reduction	Yes 3 RCTs included in MA
Ioannidou et al.[19] **2006** (US)	15/27	High	Bias not reported	Consort	7 single cohort studies and 3 RCTs but only 2 used in MA Although results favored periodontal treatment, no statistically significant differences found in CRP	Yes (only 2 RCTs)

Table 5. Primary outcomes of retained studies

Cardiovascular diseases		
Outcome 1 No relationship	**Outcome 2** Possible relationship (mixed results)	**Outcome 3** Positive relationship
Schmitt et al. 2015 (arterial stiffness) Li et al. 2017 (CV event) Ioannidou et al. 2006 (CRP)	Texeira de Freitas et al. 2012 (hsCRP) Paraskevas et al. 2008 (hsCRP)	Orlandi et al. 2014 (for endothelial function) Teeuw et al. 2014 (numerous surrogates: hsCRP in those with comorbidities; and improved endothelial function)

however the RCT did not find a statistically significant difference between the intervention and control groups whereas the cohort study results significantly favoured the treatment group. This is consistent with other findings where the lower levels of evidence reported greater effects than the higher levels. With these contradictory results, the authors concluded there was insufficient evidence that NSPT had a positive effect on reducing arterial stiffness and subsequently lowering the risk of CV events.

Orlandi and colleagues[15] included studies in their SR/MA that investigated the effects of NSPT on endothelial function, a surrogate measure for cardiovascular disease measured by flow-mediated dilation. The results of the meta-analysis that included 3 of 6 RCTs (Table 4) demonstrated statistically significant differences between the treatment and control groups following NSPT. They concluded that periodontal disease and endothelial dysfunction are causally related. Teeuw et al.[16] also reported similar findings for endothelial function as well as several other biomarkers of atherosclerosis. However, one must keep in mind that these results cannot preclude a causal relationship between periodontal disease and cardiovascular disease as endothelial dysfunction is a surrogate measure of cardiovascular disease not a direct outcome measure.

Four SR/MAs investigated the effects of NSPT on C-reactive protein (CRP), a non-specific marker of systemic inflammation that has been shown to be elevated in the presence of periodontal disease in numerous studies.[16–19] Both the Centers for Disease Control and Prevention and the American Heart Association have classified serum levels of CRP through high-sensitivity analysis to be indicators of coronary heart disease risk.[24] Thus it is hypothesized that, since periodontal disease has been shown to increase serum CRP, reducing periodontal inflammation through NSPT may reduce systemic levels of CRP and subsequently lower the risk for CV events. Results of these CRP studies were mixed. Texeira de Freitas et al.[17] reported positive results, concluding that CRP values were reduced following NSPT. However, although all 4 studies used in the meta-analysis demonstrated reductions in CRP, only 2 of the 4 studies had statistically significant outcomes. Interestingly, one of the studies that was included in the Texeira de Freitas[17] MA (Tonetti et al.[25]) was excluded in the Paraskevas MA[18] due to lack of reporting of end-of-trial means. This begs the question as to how Texeira de Freitas et al.[17] arrived at their results?

One of the key findings in the Teeuw et al. SR/MA was that NSPT reduced hsCRP only in periodontitis patients with comorbidities but not in healthy participants.[16] This finding is in direct contrast to those of Paraskevas et al.[18] who found reductions in hsCRP in healthy patients, although they categorized the level of evidence to be modest. Additionally, Ioannidou et al.'s[19] findings did not support the hypothesis that periodontal therapy reduced serum CRP.

These very inconsistent findings are not surprising given that CRP is a non-specific marker of the acute-phase inflammatory response. Elevated levels of CRP associated with periodontal inflammation are modest at best and often do not exceed the clinical normal.[18] There are many conditions that are known to raise CRP values such as obesity, smoking, and trauma; other unknown inflammatory conditions may also contribute to elevations in CRP.[26,27] These confounders are often not mentioned in clinical trials as they are difficult to control. In addition,

Table 6. Summary of issues identified by authors of systematic reviews of RCTs

1. Inconsistency in defining periodontal disease and periodontal disease severity
2. Inconsistency in the type of periodontal treatment provided, i.e., timing, frequency, clinician, use of antibiotics, etc.
3. Quality of studies (methodological shortcomings)
4. Variation in outcomes measured and measurement technique used
5. No uniform methods for adjustment of confounders (i.e., smoking, obesity, comorbidities)
6. Publication bias: studies showing no (negative) effect may not have been published
7. Only 1 study identified that used a cardiovascular event as the endpoint
8. All other studies used surrogate measures for cardiovascular disease risk

Table 7. Bradford Hill criteria results

Criteria	Met	Not met
Strength of association		X
Consistency		X
Specificity		X
Temporality		X
Dose-response		X
Biological plausibility	X	
Coherence	X	
Experiment		X
Analogy		X

there are numerous laboratory techniques for measuring high sensitivity CRP (hsCRP) and studies have not been consistent in their use of these various methods, which could contribute to inconsistencies in results.

Authors of the 7 SR/MAs identified similar shortcomings in the individual studies included in their SR/MAs. Table 6 lists common issues identified by these authors.

Using the Bradford Hill criteria for causation to determine whether a causal relationship exists between periodontal disease and cardiovascular disease, several criteria have not yet been satisfied. In examining the "strength of association," modest evidence was reported by only 2 studies for 2 different surrogate measures[15,16] (endothelial function and hsCRP). The second criterion of "consistency" has not been met as numerous inconsistencies in findings have been reported. This also poses a question as to publication bias; how many studies were turned away that did not have positive results? Similarly, the criterion of "specificity" has not been met; the studies failed to demonstrate that in every instance, the outcome will be the same. In fact, of all the studies included in this review, only one examined the effect of periodontal therapy directly on cardiovascular outcomes. All the other studies used surrogate measures. The criterion of "temporality," where periodontal disease is required to precede cardiovascular disease, has not been established, which definitely weakens the cause and effect hypothesis. Although experiments (RCTs) have been conducted, surrogate measures rather than cardiovascular events as direct outcomes following periodontal treatment have been investigated with the exception of one study.[13] Studies investigated in this review also have not demonstrated a "dose-response" outcome comparing results with various magnitudes of periodontitis, demonstrating those with more severe periodontal disease would have a greater prevalence of cardiovascular disease. The criterion of "biological plausibility," however, clearly has been met, as elevated levels of inflammatory cytokines are present during both periodontitis, and cardiovascular disease and several plausible mechanisms have been demonstrated in previous studies. The criterion of "coherence" also has been previously met as numerous biological, animal, and human studies have well established that a relationship exists between periodontal disease and cardiovascular disease. "Experiment" has failed to demonstrate consistent results through RCTs and SRs/MAs of these studies, particularly since the only positive experimental results have used surrogate measures rather than direct cardiovascular events as outcomes. Finally, the last criterion of "analogy," although the weakest, was not explored in this review. Thus, of the 9 criteria, only 2 (biological plausibility and coherence) can be said to have been fulfilled. Table 7 summarizes these results.

Therefore, based on this analysis, it is concluded that there is not sufficient evidence to support a causal relationship between periodontal disease and cardiovascular disease.

CONCLUSION

Based on findings from the 7 SRs/MAs investigated in this current review, one can state with confidence that the answer to the PICO question, "For adults in good general health who are diagnosed with periodontal disease, will receiving non-surgical periodontal therapy (NSPT), as compared to not receiving NSPT, lower their risk for cardiovascular diseases?" is "No." Current evidence does not support NSPT for reducing the rate of cardiovascular events. Numerous issues exist with published studies that may have influenced these results. Future studies will need to focus on correcting these inconsistencies, particularly by identifying 1) a standard case definition of periodontal disease, 2) the type and frequency of the intervention, 3) the target population, and 4) measuring the effectiveness of the intervention.

While it has been well established in 2 previously published CDHA position papers that an association exists between periodontal disease and cardiovascular diseases, neither of those papers investigated the nature of that association. This position paper explored the possibility that periodontal disease is causally related to cardiovascular

disease by investigating whether sufficient evidence exists that NSPT lowers the risk of a cardiovascular event. The results of this paper provide clear evidence that, although an association exists, the nature of that link remains unknown. There is insufficient evidence at this time for that association to be causal. Nonetheless, clients should continue to be provided with appropriate dental hygiene care and educated on the benefits of good oral hygiene. The results of this study will enable the dental hygiene practitioner to clarify the nature of this relationship with their clients based on the most current research.

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CONFLICTS OF INTEREST

The authors have declared no conflicts of interest.

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