Periodontal Disease and Coronary Heart Disease Incidence: A Systematic Review and Meta-analysis

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BACKGROUND: Periodontal disease is common among adults in the US and is a potential source of chronic inflammation. Recent data have suggested an important role for chronic inflammation in the development of coronary heart disease (CHD).

OBJECTIVE: To aid the United States Preventive Services Task Force (USPSTF) in evaluating whether periodontal disease is an independent novel risk factor for incident CHD.

METHODS: Studies were identified by searching Medline (1966 through March 2008) and reviewing prior systematic reviews, reference lists, and consulting experts. Prospective cohort studies that assessed periodontal disease, Framingham risk factors, and coronary heart disease incidence in the general adult population without known CHD were reviewed and quality rated using criteria developed by the USPSTF. Meta-analysis of good and fair quality studies was conducted to determine summary estimates of the risk of CHD events associated with various categories of periodontal disease.

RESULTS: We identified seven articles of good or fair quality from seven cohorts. Several studies found periodontal disease to be independently associated with increased risk of CHD. Summary relative risk estimates for different categories of periodontal disease (including periodontitis, tooth loss, gingivitis, and bone loss) ranged from 1.24 (95% CI 1.01–1.51) to 1.34 (95% CI 1.10–1.63). Risk estimates were similar in subgroup analyses by gender, outcome, study quality, and method of periodontal disease assessment.

CONCLUSION: Periodontal disease is a risk factor or marker for CHD that is independent of traditional CHD risk factors, including socioeconomic status. Further research in this important area of public health is warranted.

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BACKGROUND

Coronary heart disease (CHD) is the leading cause of death and morbidity in the US and many developed countries. In the year 2002 nearly 500,000 people died of CHD in the US, and millions of others live with prevalent CHD.[1] Worldwide, CHD kills more than 7 million people each year.[2] It is estimated that in the US in 2006, heart disease cost more than 258 billion dollars in health-related costs and lost productivity.[3] Many risk factors for CHD have been identified, but a significant proportion of CHD is not explained by traditional risk factors. Recently, several lines of evidence have implicated chronic inflammation etiologically in CHD and cardiovascular disease (CVD).[4]

Periodontal disease is a chronic gram-negative anaerobic infection of the tooth-supporting structures with an estimated prevalence of as high as 75% in adults in the US, among whom approximately 20–30% have severe forms of the disease.[5–7] Alveolar bone resorption is both a measure and a consequence of severe periodontal disease. Common signs of periodontal disease that are identified by dentists and may be noted by primary care providers include: tooth loss, gingivitis with gum inflammation and bleeding, excess tartar, infection, decay, tooth mobility, and gum recession with bone loss (Fig. 1). Periodontal disease is associated with elevations of several markers of chronic inflammation,[8–13] and because of evidence implicating chronic inflammation in the etiology of CHD, a etiologic relationship between periodontal disease and CHD has been hypothesized.[4] For these reasons, there has been strong interest in evaluating whether periodontal disease is independently associated with CHD.

In this systematic review and meta-analysis, we evaluate the epidemiologic literature evaluating the possible link between periodontal disease and associated measures of oral health, and CHD, to aid the USPSTF in their review and consideration of screening for non-traditional risk factors for CHD. Identifying individuals at higher risk for CHD than predicted by traditional risk factors could facilitate more aggressive treatment of risk factors known to decrease CHD in high-risk individuals, such as those with hyperlipidemia. Our meta-analysis differs from two prior meta-analyses[14,15] by focusing on population-based prospective studies, more recent literature, systematic evaluation of study quality and by conducting subgroup analyses to explore identified associations.

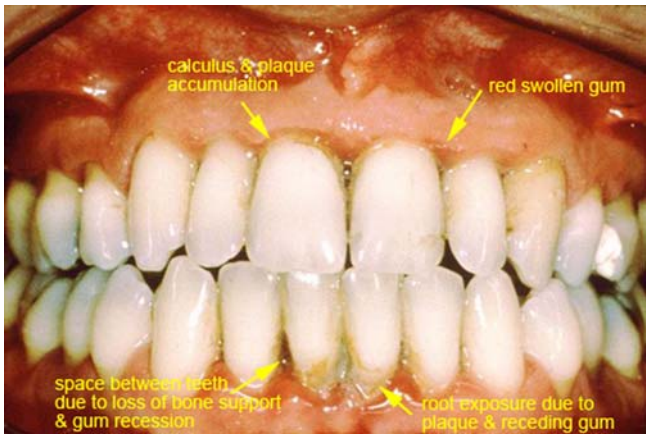

Figure 1. Common signs of periodontal disease.

METHODS

We reviewed the MEDLINE database (1966-March 2008) using the search terms cohort studies, cardiovascular diseases, and periodontal diseases. To ensure complete ascertainment, we reviewed the bibliographies of reviews, editorials, book chapters and letters discussing the relationship between periodontal disease and CHD. We sought studies evaluating the risk of CHD associated with periodontal disease in the general population and excluded studies conducted among populations with known CHD. Criteria for inclusion in the systematic review and meta-analysis were the following: prospective study with cohort or nested case control design, CHD or CVD as an outcome, and availability of English-language abstract for review. Two reviewers assessed studies for inclusion in the review. Data were abstracted by one reviewer and reviewed for accuracy by another author; any discrepancies were adjudicated by a third author.

We abstracted study data and compiled evidence tables. The focus of this review was on CHD events. However, in some circumstances papers only reported a combined estimate for all CVD events. Since most CVD is accounted for by CHD, when no other CHD-specific data were available from a study, we included these estimates in our review and meta-analysis. Studies varied in their definition of periodontal disease and the CHD and CVD outcomes they evaluated. Definitions of CHD and CVD events were taken directly from the reviewed studies. Most often, CVD mortality was defined by International Classification of Disease codes or World Health Organization criteria or included any death resulting from CHD or CVD. For this review, we categorized outcomes as follows: CHD deaths include any death attributed to CHD; CHD events include MI, coronary admission, or revascularization, and CHD death; MI was defined within each study and is a subset of CHD events; CVD events include CHD events, stroke, and peripheral vascular disease; and CVD deaths include any death attributed to CVD. When more than one study was published from the same cohort, we reviewed all of them, although only included data from the most current or informative of the studies in the meta-analysis and summary tables unless unique information was provided by another article from the same cohort.

To rate the quality of each of the studies, we reviewed all related articles describing the studies, but did not query study authors. Two investigators independently rated the quality of each study based on criteria created by the Third USPSTF;[16] discrepancies were adjudicated by a third reviewer. These criteria are shown in Table 1. After reviewing and rating the studies, we limited our formal review and meta-analyses to only studies rated as fair or good quality. In our quality ratings we gave great importance to statistical adjustment for traditional CHD risk factors since our goal was to determine whether periodontal disease is an independent risk factor for CHD.

Meta-analysis

We conducted meta-analyses to obtain a combined estimate of the association between CHD outcomes and different types of periodontal disease. We also explored whether the estimate differed with study-level variables. Because CHD outcomes were reported differently among studies, we categorized the reported CHD outcomes into four groups: CHD events, CHD death, CVD events, and CVD death, as described above. Periodontal disease, periodontitis, gingivitis, and bone loss were defined within each study and coded as present or absent and sometimes by severity or according to a standardized

Table 1. USPSTF Quality Rating Criteria for Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria
·Initial assembly of comparable groups: RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
·Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
·Important differential loss to follow-up or overall high loss to follow-up
·Measurements: equal, reliable, and valid (includes masking of outcome assessment)
·Clear definition of interventions
·Important outcomes considered
·Analysis: adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs (i.e., analysis in which all participants in a trial are analyzed according to the intervention to which they were allocated, regardless of whether or not they completed the intervention)
Definition of ratings based on above criteria
Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; appropriate attention to confounders in analysis
Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; some but not all potential confounders are accounted for
Poor: Studies will be graded "poor" if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); key confounders are given little or no attention

index; teeth were counted and categorized into groups. "Periodontal indexes" were calculated within studies and based on the presence of periodontitis, gingivitis, bone loss, and number of teeth. Risk ratios and the associated standard errors of confidence intervals were abstracted from each study. The risk ratio estimates used in the studies included odds ratio (OR), hazard ratio (HR), and rate ratio (RR).

We included all studies in the meta-analysis since they were conducted using similar methodologies and adjusted for traditional risk factors and/or other confounding variables. We stratified the analysis by different types of periodontal disease to address differences in the definition of risk factors. To account for variation among studies, a random effects model was used to combine the risk ratios. When there is no variation among studies, the random effects model yields the same results as a fixed effects model. We assessed heterogeneity by standard χ^2 tests and detected significant heterogeneity. To further examine heterogeneity, subgroup analyses were performed on study level variables such as mean duration of the study, outcome categories (CHD/CVD death and CHD/CVD events), quality rating, and gender. Sensitivity analysis was also conducted when necessary. Publication bias was evaluated using funnel plots and Egger's linear regression method,[17] and none was detected. All analyses were performed by using STATA 9.1 (StataCorp, College Station, TX, 2006).

Role of the Funding Source

This research was funded by the Agency for Healthcare Research and Quality to support the work of the US Preventive Services Task Force under contract no. 290-02-0024, task order no. 2, Rockville, MD. Agency approval was required before this manuscript could be submitted for publication, but the authors are solely responsible for its content and the decision to submit it. This analysis was conducted as part of a review of non-traditional risk factors for coronary artery disease. Prior to submission, this report was reviewed by several experts in the area of cardiovascular disease epidemiology, by USPSTF project leaders, and by AHRQ staff, and revised accordingly.

RESULTS

We reviewed 143 abstracts and identified 68 full papers from which 7 studies of fair or good quality conducted in 7 cohorts were identified. Figure 2 shows the number of articles excluded and the reasons for exclusion.

The seven cohort studies were conducted in North America and Finland and represent cohorts of 175-170,000 men and women with follow-up ranging from 5–21 years. Table 2 shows details of these studies. The definition and ascertainment of periodontal disease differed among studies, with most employing dental examinations and radiographs, and two relying on self report. The measures of periodontal disease used in the studies utilizing dental examinations included: bone loss, pockets, inflammation/gingivitis, and tooth loss. Studies identifying periodontal disease based on self report categorized periodontal disease as a history of periodontal disease or by quantifying tooth loss. Three studies[20–22] were rated of good quality, and four were fair quality.[18,19,23,24]

The association between any designation of periodontitis based on either self report or dental examinations and CHD

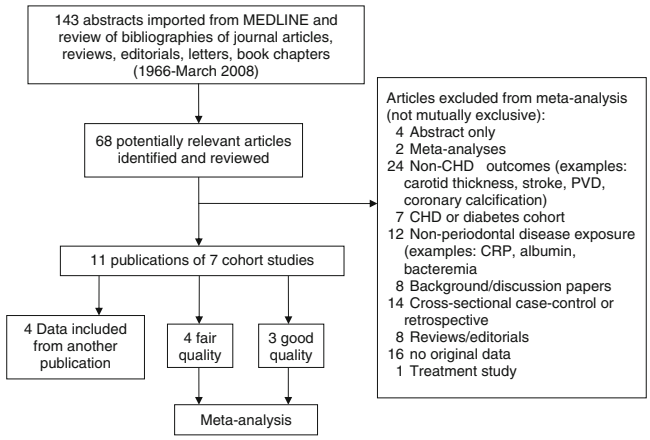

Figure 2. Search and selection of literature on periodontal disease.

was evaluated in six studies.[18–21,23,24] Baseline periodontal disease was significantly associated with an increased risk of CHD in three cohorts[18–20], and three showed no significant association.[21–24] When these studies were combined in meta-analysis, the summary estimate of risk ratio was 1.24 (95% confidence interval 1.01–1.51) for any CHD or CVD event as shown in Figure 3. Significant heterogeneity was detected across studies (P=0.04) and incorporated into the combined estimate based on the random effects approach.

Tooth loss is considered a consequence and another form of periodontal disease. Five studies[18,20,22–24] compared individuals by evaluating tooth loss at baseline as a measure of periodontal disease, and four studies[18,20,22,23] either showed or suggested an increased risk of subsequent CHD among individuals with higher baseline tooth loss. In one good quality study conducted among approximately 100,000 health professionals in the US, baseline number of missing teeth was directly related to CHD events/death, with a suggestion of a dose response relationship.[22] Another good quality study identified a 23% increased risk of CHD among individuals who were edentulous at baseline after adjustment for all Framingham risk factors, as well as education, marital status, and poverty index.[20] Only one study suggested a negative association between being edentulous and CHD death,[24] and it is not clear why the results were inconsistent with other studies. When all these studies were combined in a meta-analysis, the summary estimate for all CHD/CVD events was 1.34 (95% CI 1.10–1.63), indicating a 34% increased risk of CHD or CVD events among individuals with 0–10 teeth at baseline compared with 25–32 teeth (Fig. 3). There was significant heterogeneity among studies (P=0.02). A sensitivity analysis excluding Tuominen's study yielded a combined estimate of 1.41 (95% CI 1.22 –1.63). Also, heterogeneity among studies became non-significant when this study was excluded (P=0.198).

Gingivitis as a measure of periodontal disease was evaluated in two cohorts,[20,23] and both showed or suggested elevated rates of CHD death among individuals with baseline gingivitis. When combined in meta-analysis, the summary estimate was 1.35 (95% CI 0.79–2.30) (Fig. 3). Bone loss was an important risk factor for subsequent CHD in the one study evaluating this potential risk factor, with relative risks of 1.50 (95% CI 1.04–2.14) and 1.9 (95% CI 1.10–3.32) for total and fatal CHD, respectively.[19]

Table 2. Studies of Periodontal Disease and Coronary Heart Disease

Study (quality rating)	Demographics	Dental assessment method; exposures measured	Follow-up (years); loss to follow-up (%); outcomes studied; outcome assessment	Variables adjusted for	Baseline prevalence of periodontal disease (%)
Helsinki Aging Study[18] (fair*)	175 M and F ages 78–85	Dental exam; PD, tooth loss	5; <2%; mortality, CVD mortality; Finnish Death Registry	Age, sex, TC, HDL, BP, smoking, BMI, prevalent CHD, social class	Periodontitis: 46
Dental Longitu-dinal Study VA[19] (fair*†)	1,094 M veterans ages 21–81 (mean 42.7), free of known chronic illnesses	Radiographic and dental exams: PD, bone loss, clinical probe depth	18; NR; Total CHD (MI, CHD death, angina), stroke	Age, BMI, smoking, sBP, dBP, TC, family history of CHD, alcohol	Mean bone loss score >1: 21 periodontitis: NR
NHANES[20] (good)	9,760 M and F ages 25–74 without known CHD	Dental exam; no. decayed teeth, periodontal clas-sification and index, oral hygiene index, no. teeth	14; <10%; CHD and total mortality, CHD admission; death certs, medical records, interviews	Age, sex, race, education, marital status, sBP, TC, BMI, DM, activity, alcohol, poverty index, smoking	Gingivitis: 23 Periodontitis: 18 Edentulous: 22
PHS[21] (good)	22,037 M physicians ages 40–84 without stroke, MI, TIA, or cancer	Self report; tooth lossPD	12; <1%; stroke, all CVD, CV death, non-fatal MI, annual surveys, medical record review	Age, sex, smoking, DM, BP, BMI, exercise, alcohol	Periodontitis: 12
Health Profes-sional Follow-up Study, NHS[22] (good)	Health professionals; 41,407 M ages 40–75; 58,974 F ages 30–55; healthy at baseline	Self report; history of PD no. teeth history of bone loss	Women ≤20, men ≤12;<10%; CHD including fatal CHD, SCD, MI; death certs, hospital records	Age, sex, TC, smoking, DM, BP, BMI, exercise, alcohol, FMH, MVI, vit E, menopausal, HRT use	<=10 teeth: 7 <=16 teeth: 21
Nutrition Canada Survey[23](fair*†)	4,248 M; 5,083 F ages 35–84 without CHD or CVD; median age 40	Dental exam; edentulous, periodontitis, gingivitis	≤21 years; 23%; mortality, CHD mortality;Canada National Mortality Data	Age, sex, TC, smoking, DM, HTN, province	Gingivitis: 40 Periodon titis: 12 Edentulous: 26
Mini Finland Health Survey[24] (fair*)	3,091 M; 3,436 F aged 30–69; representative of Finnish population	Dental exam; edentulous, periodontitis treatment	12 years; NR; CHD death; Statistics Finland	Age, sex, TC, smoking, DM, BP	Edentulous: 19 Periodontitis: 25

Less adjustment for cardiovascular risk factors

†Unclear or >20% loss to follow-up

Abbreviations: BMI=body mass index, BP=blood pressure, CHD=coronary heart disease, CV=cardiovascular, CVD=cardiovascular disease, DM=diabetes mellitus, F=females, FMH=family history, HDL=high density lipoprotein, HRT=hormone replacement therapy, HTN=hypertension, M=males, MI=myocardial infarction, MVI=multivitamin, NHANES=National Health and Nutrition Examination Survey-I, NR=not reported, PD=periodontal disease, SCD=sudden cardiac death, TC=total cholesterol, TIA=transient ischemic attack, vit E=vitamin E.

Since tests of heterogeneity showed significant heterogeneity among studies, we examined this with several subgroup analyses. These analyses are shown in Figure 4. First we tested whether results varied by the method used to measure periodontal disease. Among the five cohorts relying on dental examination at baseline to measure periodontal disease, four[18–20,23] showed an increase in CHD events among those with more significant periodontal disease and/or tooth or bone loss at the baseline exam. The combined estimate of risk ratio for CHD/CVD events was 1.39 (95% CI 1.19–1.62) for dental examination studies. Only two studies relied on self report of periodontal disease, of which one showed increased risk[22] and the other did not;[21] when combined the summary risk ratio was 1.30 (95% CI 0.96–1.76), suggesting an association but not statistically significant. Notably, approximately 24% of the subjects were dentists in the study showing a relationship between self-reported periodontal disease and CHD.[22]

Results of other subgroup analyses showed very little difference in risk by outcome, with an estimated risk ratio of 1.28 (95% CI 0.94–1.73) for CHD or CVD death when studies were combined that only reported CHD or CVD death, and 1.34 (95% CI 1.08–1.66) for CHD or CVD events when studies were combined that only reported CHD or CVD events. Risk estimates for all CHD or CVD events varied by gender, with higher risk associated with periodontal disease among women (summary risk ratio 1.59 (95% CI, 1.28–1.96), compared with 1.23 (95% CI, 0.92–1.64) among men), although these differences were not statistically significant. The combined estimate for both genders was 1.31 (95% CI 1.08–1.59). Another consideration in our subgroup analysis was whether the risk ratios varied with length of follow-up. We dichotomized the length of follow-up as ≤15 years, or >15 years, and the summary estimate of risk ratio for follow-up of ≤15 years was 1.19 (95% CI 1.02–1.40) and for over 15 years was 1.67 (95% CI 1.27–2.20). The difference between the risk estimates was significant at the 0.05 level (p=0.022). Finally, the risk estimates did not differ with quality rating [RR=1.45 (95% CI 1.26–1.66) for good quality versus 1.30 (95% CI 0.96–1.76) for fair quality studies] (Fig. 4).

	Outcome	Number of Subjects*	Risk Factor Measurement	Quality	Gender	Followup (in yrs)	RR (95% CI)
Risk Factor = Periodontitis							
Morrison, 1999	CHD Death	2297	Dental exam	Fair	B**	21	1.37 (0.80, 2.35)
Tuominen, 2003 (M)	CHD Death	2518	Dental exam	Fair	M**	12	1.00 (0.61, 1.63)
Tuominen, 2003 (F)	CHD Death	2392	Dental exam	Fair	F**	12	1.18 (0.60, 2.31)
DeStefano, 1993	CHD Events	5041	Dental Exam	Good	B	14	1.25 (1.06, 1.48)
Beck, 1996	CHD Events	1221	Dental Exam	Fair	M	18	3.10 (1.30, 7.40)
Ajwani, 2003	CVD Death	175	Dental Exam	Fair	B	5	2.28 (1.03, 5.05)
Howell, 2001	CVD Events	22037	Self report	Fair	M	12	1.01 (0.88, 1.15)
Periodontitis Studies Combined							1.24 (1.01, 1.51)
Risk Factor = 0-10 teeth							
Morrison, 1999	CHD Death	3330	Dental exam	Fair	B	21	1.90 (1.17, 3.10)
Tuominen, 2003 (M)	CHD Death	1510	Dental exam	Fair	M	12	0.90 (0.50, 1.60)
Tuominen, 2003 (F)	CHD Death	1479	Dental exam	Fair	F	12	0.30 (0.10, 1.00)
DeStefano, 1993	CHD Events	5398	Dental Exam	Good	B	14	1.23 (1.05, 1.44)
Hung, 2004 (M)	CHD Events	41407	Self report	Good	M	12	1.36 (1.11, 1.67)
Hung, 2004 (F)	CHD Events	58974	Self report	Good	F	20	1.64 (1.31, 2.05)
Ajwani, 2003	CVD Death	175	Dental Exam	Fair	B	5	1.46 (0.69, 3.09)
Combined excluding Tuominen							1.41 (1.22, 1.63)
Studies of 0-10 Teeth Combined							1.34 (1.10, 1.63)
Risk Factor = Gingivitis							
Morrison, 1999	CHD Death	3921	Dental exam	Fair	B	21	1.82 (1.24, 2.68)
DeStefano, 1993	CHD Events	5537	Dental Exam	Good	B	14	1.05 (0.88, 1.26)
Gingivitis Studies Combined							1.35 (0.79, 2.30)

* Number of subjects included in the analysis
** Abbrevations: B, Both gender; M, Male; F, Female.

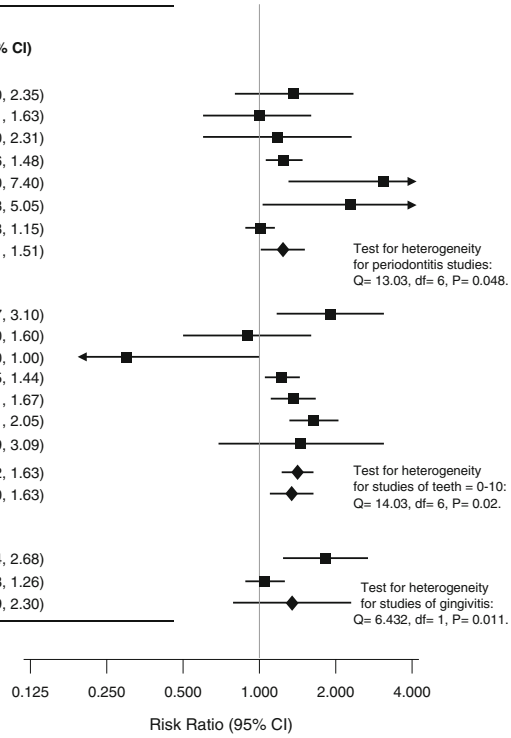

Figure 3. Meta-analysis of combined studies.

DISCUSSION

Our systematic review and meta-analysis evaluating the relationship between periodontal disease, including gingivitis, bone loss, and missing teeth, suggests that periodontal disease is an independent, though relatively weak, risk factor for CHD. Our analyses provide the most current measure of the association between periodontal disease and CHD, and suggest that various measures of periodontal disease confer approximately a 24–35% increase in risk of CHD.

Our study focuses on prospective studies conducted among the general population rather than combining data from referral centers or cohorts with known CHD, which allows for evaluating cause/effect relationships and for generalizing our results to other populations. Also, given that these are very large populations followed for CHD, a very common cause of morbidity and mortality in North America and Europe, it is unlikely that knowledge of periodontal disease biased the ascertainment of CHD. Thus, our meta-analysis results suggest either a biological link or unknown confounding with periodontal disease serving as a marker for subsequent CHD. While we believe our findings provide a more current measurement of the association between periodontal disease and CHD than prior systematic reviews and meta-analyses, it is notable that our findings are similar to older meta-analyses that have shown summary relative risks in the 1.15 to 1.19 range.[14,15]

There are several limitations of our review. First, we relied on each study's definition and diagnosis of CHD. As stated above, there is no indication that bias in ascertaining outcome played a role in our findings, due to the prospective nature of the included studies. It is more plausible that exposure misclassification resulted in under-estimation of the true risk associated with periodontal disease. This is particularly likely in studies relying on self report of periodontal disease. Another limitation is incomplete adjustment for all Framingham risk factors in some of the studies. However, in a subgroup analysis of the good quality studies with adjustment for all Framingham risk factors, an independent association between periodontal disease and CHD was identified. Another limitation of our review is the relatively low number of studies evaluating the relationship, although the total number of subjects enrolled in these studies was large (approximately 227,000). Finally, each of

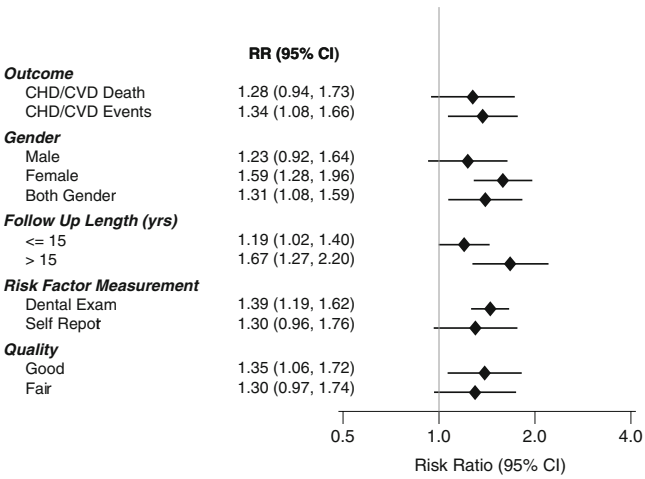

Figure 4. Subgoup analyses.

the studies evaluated periodontal disease differently, although most involved a dental examination.

We believe our review is strengthened by only including studies in which the exposure of periodontal disease was determined systematically at the beginning of the study. Furthermore, we evaluated the importance of periodontal disease in the general population rather than in populations selected for coronary artery disease which, by design, represent survival cohorts and address secondary rather than primary prevention. Although we did not systematically review literature evaluating this relationship among individuals with prevalent CHD, studies among those cohorts have also shown an association between periodontal disease and CHD.[26–28] These studies support our findings, but are limited by the issues discussed above, and their results may not be generalizable to the healthy adult population.

We also identified several case control[26,28–30] and cross-sectional[26,29–31] studies that evaluated the association between CHD and various measures of periodontal disease; most have shown a strong positive association after adjustment for many or all Framingham risk factors, as well as socioeconomic status.[32–35] The consistency of these studies with our findings lends support to the identified relationship between periodontal disease and CHD.

There are several biological mechanisms by which periodontal disease might be etiologically associated with CHD. First, studies have suggested that periodontal disease represents a chronic infection resulting in a chronic inflammatory state.[8] This hypothesis is supported by many studies showing fibrinogen, CRP, serum amyloid A and Von Willebrand factor elevations in association with periodontal disease.[11,13,18,36–38] Notably, periodontal treatment studies have shown improvements in measures of systemic inflammation such as CRP and serum IL-6 with treatment.[39] Recently, a randomized controlled trial conducted among individuals with periodontal disease showed that intensive periodontal treatment resulted in improvement of endothelial function 6 months after therapy.[40]

A second biological consideration is the intermittent bacteremia associated with periodontal disease and its possible role either in the chronic inflammatory state or more directly on endothelial tissue surfaces.[41] For example, in one study, 80% of carotid endarterectomy specimens were positive for one or more PCR assays of various oral pathogens.[41] In addition, data from the prospective ARIC study have shown that carotid artery intima-media wall thickness was associated with severe periodontal disease;[42] others have shown this as well.[43] While not statistically significant, data from a sub-sample of the ARIC study showed a relationship between periodontal disease and coronary artery calcification by CT (relative risk 1.51; 95% CI 0.54–4.23) after 2–4 years of follow-up.[44] Third, some studies have shown increased platelet activation in vivo in association with periodontal disease, which could contribute to plaque instability and thrombosis.[45] Fourth, studies conducted among animals have shown an association between atheroma formation and exposure to periodontal pathogens.[46]

Periodontal disease has also been implicated as a risk factor for stroke[23,47,48] as well as carotid atherosclerosis.[49,50] Several of the studies evaluating this outcome were conducted among cohorts included in this review and showed relative risks for stroke in association with periodontal disease in the range of 1.2 to 3.0.[14,23,51] In addition, a relationship has been shown among individuals with peripheral vascular disease and periodontal disease, as well as tooth loss.[22,52] Furthermore, data from angiography studies have shown a relationship between the extent of atherosclerosis and the degree of periodontal disease.[35] Finally, several studies have shown a relationship between oral health and total mortality.[18,20,53] These data support the role of periodontal disease in generalized atherosclerosis and support our finding of an association between periodontal disease and CHD.

If periodontal disease is not causally related to CHD, our data suggest it may be a marker of risk. This hypothesis implies that unexplained confounding by a factor associated with both periodontal disease and CHD explains the relationship. The most likely known contenders include: smoking, diet, diabetes and socio-economic factors.[54–56] However, almost all of the studies included in our review adjusted for all of these factors and still identified increased risk. In fact, three good quality studies[20,22,25] from two cohorts and one fair quality study[18] with adjustment for the traditional Framingham risk factors, plus alcohol and measures of socioeconomic status, identified significant elevations of risk. Some investigators have hypothesized that genetic susceptibility to a strong inflammatory response mediates both CHD and periodontal disease.

To clarify the link between CHD and periodontal disease will require a consistent body of evidence from longitudinal studies with standardized measures of periodontal disease and careful follow-up. The ideal longitudinal study would start in childhood and account very carefully for socioeconomic status since this CHD risk factor could confound the identified relationship. From a public health perspective, if further studies consistently identify periodontal disease as a risk factor for CHD and treatment studies show benefit, the implications are significant since periodontal disease is mostly avoidable and treatable when not prevented. In addition, good preventive dental care has multiple other benefits, particularly on quality of life. Furthermore, identifying individuals at higher risk for CHD than predicted by traditional risk factors could facilitate treatment of risk factors known to decrease CHD events in high-risk individuals, such as those with hyperlipidemia.

To definitively establish an etiological link between periodontal disease and CHD will require randomized controlled trials in which individuals are randomized to treatment versus usual care of periodontal disease and followed carefully for CHD. However, there are important ethical considerations as well as feasibility issues related to a randomized trial of an intervention known to be of benefit for reasons other than the question under study. Notably, however, such a trial is underway in a cohort of individuals with prevalent CHD.[57,58] If randomized treatment trials for primary prevention are planned, it is important to consider that short-term trials may not definitively answer the etiologic question as it is plausible that long-term exposure to periodontal disease might be more predictive of subsequent CHD. Thus, the best intervention trial would be one that began in early childhood rather than adult life. In its absence, however, if benefit were shown in an adult primary prevention treatment trial, the potential impact on public health and specifically CHD might be significant given the high prevalence of periodontal disease in the population and the common problem of CHD.

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