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The influence of prevalent cohort bias in the association between periodontal disease progression and incident Coronary Heart Disease

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ABSTRACT:

Purpose: In longitudinal studies, the onset of the index condition (e.g. exposure) does not always coincide with the start of a study's observation period, leading to the possibility of bias in estimation that derives from studying prevalent exposure rather than new exposure. We investigate the possible role of this bias in the relationship between periodontitis progression and Coronary Heart Disease (CHD) among a cohort of men participating in the Veterans Administration Dental Longitudinal Study.

Methods: At baseline, there were 298 men with existing (i.e., prevalent) periodontitis. During follow-up, routine dental inspection identified 163 new (i.e., incident) cases of periodontitis. Change in mean alveolar bone loss score (MBLS) served as the measure of disease progression. Tabular analyses were performed to obtain crude, stratified and adjusted measures of the association for periodontitis cases overall and separately for prevalent and incident cases. Potential bias was evaluated by comparing estimates across these sub-cohorts. **Results:** Among all periodontitis cases, increasing MBLS was associated with increasing risk of CHD event. Subdividing periodontal cases into new and prevalent cases revealed that the relationship was most pronounced among incident periodontitis cases (IRR for MBLS change $>0.5 = 5.4$), compared with prevalent cases (IRR for MBLS change $>0.5 = 2.5$). **Conclusions:** Studying prevalent cases of periodontitis underestimates the association between incidence periodontitis and CHD.

MeSH heading key words: Periodontal Diseases, Cardiovascular Diseases, Bias (Epidemiology), Cohort Studies

ABBREVIATIONS/ACRONYMS:

CHD	Cardiovascular/Coronary Heart Disease
CI	Confidence Interval
CSI	Comprehensive Smoking Index
DLS	Dental Longitudinal Study
ECG	Electrocardiogram
EMM	Effect Measure Modification
ICD	International Classification of Diseases
IRD	Incidence Rate Difference
IRR	Incidence Rate Ratio
MBLS	Mean Bone Loss Score
mg/dL	milligrams per deciliter
MI	Myocardial Infarction
NAS	Normative Aging Study
SD	Standard Deviation
SES	Socioeconomic Status
VA	Veterans Administration

INTRODUCTION

Periodontal disease, also known as periodontitis, is a chronic, inflammatory and progressive oral condition affecting the gums, ultimately resulting in tooth loss. Caused by the spread of bacteria below the gum line, the inflammatory process is characterized by pocketing and detachment of the connective tissue supporting the teeth, and the break down and loss of the alveolar bone surrounding the teeth. Periodontitis is primarily a condition of adulthood and aging. Prevalence estimates among worldwide adult populations aged 35-54 average around 25%, increasing sharply with age [1].

In the last 20 years, there has been a heightened interest in the relationship between periodontitis and cardiovascular conditions [2]. Proposed causal mechanisms include a direct effect of periodontal infection through bacteremia and an indirect effect of the inflammation that accompanies periodontitis (e.g. resultant increases in C-reactive protein) [3]. Non-causal pathways have included discussions of a potential genetic pro-inflammatory susceptibility that increases the risk of both conditions [4, 5].

Since the initial work conducted in the 1980's suggesting a possible role of periodontitis in the development of Coronary Heart Disease (CHD) [6, 7], several additional studies have been conducted, yet findings are inconsistent [8-10]. The inconsistency may be due, in part, to differing methods of ascertainment and case definitions, but it may also be affected by biases resulting from the evaluation of a prevalent condition [4, 11-16]. Despite inconsistencies, the association is supported by the weight of the accumulating evidence and its biologic plausibility [13, 17, 18].

Few longitudinal studies of periodontitis exist. Longitudinal study poses challenges, including the handling of tooth loss and the choice of a measure for

periodontitis. Periodontal measures based on the inflammation of the soft tissue, assessed by pocket depth and attachment loss, are problematic, owing to their fluctuation over time and from tooth to tooth. Radiographic measures of alveolar bone loss are less sensitive to local conditions, but few studies have used serial radiographs, owing to the burden and expense of equipment compared with other methods.

The general lack of longitudinal studies and the chronic nature of periodontitis often necessitate the study of prevalent periodontitis, rather than incident periodontitis. Studying a prevalent exposure, rather than an incident one, however, has been shown to result in a bias for some causal effects that change with time [16]. With the recent and ongoing trend to study periodontitis as a risk factor for other systemic diseases, it is important to understand the potential influence of studying prevalent periodontitis rather than incident periodontitis. This type of bias has not been previously studied for periodontitis.

We studied white men with periodontitis in the Veterans Administration (VA) Dental Longitudinal Study (DLS). Full-mouth radiographs, obtained on repeated visits, provided a measure of ABL, and we examined the possibility for bias in the potential association between increases in mean alveolar bone loss and increased risk of first occurrence of CHD events. Human subject research approvals were obtained from Institutional Review Boards of the VA and Boston University Medical Campus.

METHODS

The parent study for the DLS is the VA Normative Aging Study (NAS), an ongoing closed-panel prospective study of aging, which began in the 1960s [19]. At baseline, 2,280 men aged 21 to 84 years who were free of chronic disease and lived in

the greater Boston metropolitan area were enrolled. Subjects were not VA patients and received both medical and dental care in the private sector. Triennially, NAS physicians conducted thorough medical assessments. In 1968, 1,231 NAS participants volunteered to enroll in its dental component [20]. Of these, 127 never returned after baseline and 63 were edentulous, leaving 1,104 available for dental follow-up. DLS subjects received comprehensive oral examinations, including full-mouth radiographs triennially and were overwhelmingly untreated for periodontitis according to self-report (<5% of total cohort). Only 51 subjects were lost to follow-up for reasons other than death.

Periodontitis study population

The cohort of DLS subjects (also concurrent NAS subjects) provided the base population for selection into the periodontitis cohort. Eligibility for entry was based on presence of periodontitis, as determined by a Schei Score of greater than 20% loss of the alveolar bone on two or more eligible teeth (Schei Score ≥ 2). The Schei Score was measured on each tooth from the radiographic film obtained from each study follow-up by superimposing a graduated ruler along anatomical landmarks (e.g. root apex and cemento-enamel junction) [21]. Thus, the periodontitis cohort comprised both individuals who met the criterion at the DLS baseline (prevalent periodontitis) and those who met the criterion later during DLS follow-up (incident periodontitis). In other words, the periodontitis cohort represents a dynamic cohort compiled across 30 years (1968-1998) of DLS follow-up where the condition is measured from the first observation of periodontitis as defined by the Schei Score criterion. Subjects became eligible for the present analysis at the follow-up exam immediately after the Schei Score criterion was

met. Subjects were then followed until the incidence of CHD, death, the end of follow-up in the underlying cohort (DLS) or loss to follow-up.

Men were excluded from the present analysis if they developed periodontitis before age 31 or after age 60 (n=209). Follow-up was discontinued when study participants reached their 75th birthday. Men were also excluded if they did not have a minimum of eight eligible teeth with less than 60% alveolar bone loss (n=331) at the start of the exposure period. Third molars (wisdom teeth) and canines were excluded, leaving a maximum of 24 eligible teeth for observation. History of the CHD outcome (n=83) or no follow-up exams after entry (n=20) also resulted in exclusion. The study population comprised 461 men.

Data collection

Data for the study were obtained as part of the triennial DLS and NAS study visits.

Assessment of periodontitis progression (exposure). Radiographs of the teeth were taken using a cephalostat to standardize positioning. Schei Scores were assigned at two interproximal sites (mesial and distal) for each tooth in increments of 20% by a blinded periodontist (reproducibility is presented elsewhere) [22, 23]. Scores, therefore, ranged from zero to five, with zero indicating no bone loss.

Progression was characterized at each follow-up exam by total positive change in mean bone loss score (MBLS) since periodontitis onset. The periodontitis exposure measure also accounted for the loss of teeth after entry by retaining the last observed Schei Scores whenever a tooth was lost over the intervening follow-up period. The

periodontitis exposure was categorized according to MBL change: 0 (reference group), $>0 - \leq 0.25$, $>0.25 - \leq 0.5$ and >0.5 .

Outcome Identification. CHD events were ascertained independently as part of the NAS using the same criteria as that employed in the Framingham Heart Study, defined as myocardial infarction (MI), angina pectoris and fatal CHD [24]. MI was diagnosed based on ECG findings, elevation of serum enzymes and chest discomfort consistent with MI, or autopsy. Angina pectoris was defined as recurrent chest discomfort related to exertion or excitement lasting up to 15 minutes that was responsive to rest or nitroglycerin. Fatal CHD was defined as a primary cause of death attributed to CHD based on ICD-8 codes (410-414). Outcomes were assessed at each visit.

Covariates. Covariates of possible interest included body mass index, diabetic diagnosis, heavy alcohol use, socioeconomic status (SES) and smoking history. Aside from SES, covariate data were obtained at each visit. Subjects were classified as diabetic if they met any of the following criteria: 1) physician diagnosis of diabetes, 2) fasting glucose level ≥ 126 mg/dL, or 3) two hour glucose tolerance test ≥ 200 mg/dL. Heavy alcohol use was ascertained from responses to the Cornell Medical Index Health Questionnaire question, "Do you usually drink 2 or more alcoholic drinks per day?". Household incomes were obtained via self-report and used as an indicator variable for SES in analysis. Detailed smoking histories included information on duration, intensity and time since cessation. Smoking cessation was common; therefore, a continuous measure of cumulative smoking exposure, the Comprehensive Smoking Index (CSI), was calculated and categorized. The CSI provides a single measure of smoking

exposure that accounts for intensity, duration and time since cessation by utilizing the exposure half-life on the risk of developing a particular outcome [25, 26]. The half-life parameter for periodontitis has been developed previously [27]. The continuous CSI variable was dichotomized to reflect the presence or absence of remaining smoking exposure.

Statistical Analyses

We conducted a tabular analysis to estimate incidence rate ratios (IRR) and differences (IRD) and the accompanying 95% confidence intervals (CI) of the relationship between change in MBLs from periodontitis onset and first CHD event. The calculation of person-time began from the initiation of subject follow-up (e.g. identification of periodontitis) and person-time was allocated to each category of the exposure and covariates in a time-dependent fashion. Stratified analyses were conducted to assess potential effect measure modification (EMM) and confounding by covariates. Potential confounding by a covariate was assessed by comparing the crude estimate to the summary estimate obtained from stratified data (standardized morbidity ratio) and applying a 10% change-in-estimate criterion [28]. EMM was assessed by comparing stratum-specific estimates. The ability to assess EMM was limited for some stratification variables owing to the lack of CHD events in certain exposure categories.

To assess the potential presence and influence of bias in the association of incident periodontitis progression, we compared results of prevalent periodontitis subjects with those who had newly developed periodontitis at entry.

RESULTS

Characteristics of the periodontitis cohort at baseline are displayed in Table 1. Columns are included to illustrate subject characteristics according to whether they had prevalent or incident (newly developed) periodontitis at entry into the study population. On average, subjects in the periodontitis cohort were 50 years of age, had 80% of their eligible teeth remaining with less than 20% bone loss on average, and more than half of all subjects reported current or former smoking according to the CSI. Compared with those who had incident periodontitis, subjects with prevalent periodontitis were younger, had fewer teeth and more severe and extensive periodontitis at baseline. They were also more likely to have been current or former smokers, to report heavy alcohol use and displayed shorter follow-up times.

Crude, adjusted and age-stratified estimates for the studied association among the overall periodontitis cohort are presented in Table 2. Increases in MBLS appeared to result in increasing rates of CHD. Compared with the unexposed population (no change in MBLS), increases in MBLS since periodontitis onset of greater than 0.25 and 0.50 were associated with two-fold and three-fold increases in the rate of CHD, respectively (IRR=2.2; 95% CI: 1.1, 4.1, IRR=3.3; 95% CI: 1.8, 6.2). There was no evidence of confounding by a covariate for any exposure category according to the change-in-estimate criterion (Table 2 shows estimates when smoking was adjusted for, other data not shown). Stratum-specific estimates revealed heterogeneity according to age at first observation of periodontitis (age at onset) with younger subjects experiencing greater relative and absolute increases in the rates of CHD.

Stratified analyses aimed at identifying the presence and influence of prevalent cohort bias are presented in Table 3. Stronger crude associations were observed

among those with incident periodontitis compared with those who had prevalent, indicating that a bias may be present in the results of the overall cohort. Specifically, analyses of the highest exposure category resulted in an observed estimate among subjects with incident periodontitis (IRR=6.8; 95% CI: 1.8, 26) that was nearly three times higher than that observed among subjects with prevalent periodontitis (IRR=2.5; 95% CI: 1.2, 5.0). P-value functions depicting these associations can be viewed in Figure 1. Further investigation of only that subset of subjects who had incident periodontitis indicated the presence of positive confounding by age at periodontitis onset and cigarette smoking, as well as a change in the direction of EMM by age at periodontitis onset (Table 4).

DISCUSSION

The primary aim of this study was to investigate the potential role of bias in estimates obtained from the evaluation of a prevalent and progressive condition—periodontitis. Studies of the association between periodontitis and CHD outcomes have been conducted previously [29]. However, this study is the first to examine periodontitis progression as a predictor and to study it among a population of individuals suffering from periodontitis. This design provided the present opportunity to assess the difference in the observed associations as a result of including subjects whose periodontitis onset occurred before the start of the base population's follow-up (DLS)—also known as prevalent cohort bias [16].

The strength of the relative associations that we observed in the overall periodontitis cohort were similar to those observed by others who have evaluated prevalent periodontitis with respect to CHD outcomes [24, 29, 30], including within the

DLS subject population [5]. The inclusion of subjects with prevalent periodontitis, however, appears to have resulted in lower estimates than those seen for persons with incident periodontitis. When analyses were restricted to those with newly developed periodontitis at the start of the observation period, we observed adjusted relationships of two, three and more than five-fold increases in the rate of CHD with each increasing exposure category (Table 4)—twice the size of the respective associations observed among those with prevalent periodontitis at entry (Table 3). Additionally, the assessment of EMM by age at onset in the overall cohort suggested that the measures of association were reduced among older subjects compared with younger subjects. However, the opposite was observed among subjects with incident periodontitis—a finding which contradicts several investigations of prevalent periodontitis [13], including those conducted among the DLS population [4, 31].

Prevalent cohort bias [16] is a special case of ‘left truncation’ [32, 33] in which otherwise eligible subjects are not observable for study due to experiencing a disqualifying event prior to the start of follow-up. Left truncation is a potential source of ‘selection bias’ [33, 34], with the underlying mechanism most simply attributed to the fact that there is a difference between those individuals who made it into the observation period and those who did not [35]. In the case of our prevalent cohort, those who had periodontitis before study baseline may have experienced CHD-related mortality, a disqualifying CHD event, or left the study base, before the start of follow-up, and they are not represented in our study population. On the other hand, those with prevalent periodontitis at baseline who were included in our analysis specifically did not experience any of those events before baseline (e.g., free of the outcome at baseline);

therefore, the prevalent periodontitis subjects included in the present analysis may be different from those in the DLS with periodontitis who did not make it into this study. They are additionally different from those who enter the observation period concurrent with new development of periodontitis. The effect of this bias mechanism is similar across disciplines of epidemiology (e.g., occupational) in that those with prior exposure who make it into the study follow-up are most often younger at entry, older at the time of the outcome, display longer follow-up times and have higher exposures, often leading to an attenuation of the observed association [32] as well as a loss of precision [33].

In the present study, similar differences in the exposure characteristics to those referenced above were observed (see Table 1). Additionally, among the unexposed (no change in MBLs), the incidence rate of CHD was nearly four times as high among those with prevalent periodontitis than among those with incident periodontitis, indicative of potential truncation by missing person-time at risk (Table 3). The severity of periodontitis (overall MBLs) among the unexposed was also greater for subjects with prevalent periodontitis. In fact, the MBLs observed among those unexposed in the prevalent cohort was nearly equivalent to that observed among those with incident periodontitis who had experienced an increase in MBLs of greater than 0.25 (see Table 3). Therefore, the strength of the observed relative rates is reduced among prevalent periodontitis cases.

Previous findings related to EMM by age on the ratio scale can be similarly attributed to this mechanism. Dietrich et al recently reported on age-dependent associations between periodontitis (MBLS at each interval) and incident CHD in the DLS cohort where similar heterogeneity by age was observed, leading the authors to

conclude that periodontitis was associated with CHD among younger men only [5]. Calculations of the data presented in the Dietrich et al study revealed similar findings to ours when the incidence rate of CHD among older men who were deemed 'unexposed' was found to be three times higher than the respective rate of CHD among younger men. In our study, the baseline incidence rates of CHD in the overall periodontitis cohort are higher for older subjects, thereby reducing the size of the relative and absolute measures in that subgroup. However, when analyses were restricted to those with newly developed periodontitis, the same heterogeneity in the measures of association according to age at onset was not observed. Given that periodontitis is known to be a disease of aging, it seems reasonable that age at onset may serve as a proxy for prevalent or preexisting periodontitis and as such may exert the same influences on valid estimation.

These and similar effects of bias in prospective cohort studies of long-term and prevalent exposures have frequently been identified in occupational epidemiology [32, 36, 37], pharmacoepidemiology [38], HIV seroconversion [39], reproductive [40], and other branches of epidemiology. A recent simulation study showed that the inclusion of individuals with prevalent exposure (i.e. prevalent hires) at baseline introduced a downward bias in estimates for null and positive associations [32]. The authors noted that the extent of the bias possible is likely a function of how long they had been exposed before the start of follow-up, which is often unobservable.

This work primarily serves to highlight the influence of prevalent and progressive conditions on valid estimation when their potential effects are under study. Current methods for addressing these influences are limited. As observed in the current

research, restricting to those in the incident cohort may reduce information and the prevalent cohort may still yield useful information for those who are not part of an inception cohort. Lastly, the results of the present study among those subjects with newly developed periodontitis at entry indicate that progression is associated with an increased incidence of CHD more strongly than previously reported in the literature. The strength of the associations may additionally depend on a person's age at onset of periodontitis.

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Table 1. Baseline Characteristics of Men With Periodontitis According to Periodontitis Status at Entry

Baseline Characteristic	Periodontitis Cohort		
	Overall (n=461)	Prevalent (n=298)	Incident (n=163)
Age at onset [mean (years \pm SD)]	49.6 \pm 6.6	48.5 \pm 6.8	51.5 \pm 5.6
Follow-up Time [mean (years \pm SD)]	13.0 \pm 3.7	12.8 \pm 3.6	13.5 \pm 4.0
No. Eligible Teeth (mean \pm SD)	19.2 \pm 3.5	18.8 \pm 3.5	20.0 \pm 3.5
Mean MBLS (mean \pm SD)	0.85 \pm 0.37	0.94 \pm 0.4	0.68 \pm 0.2
No. Teeth with \geq 20% ABL (mean \pm SD)	4.6 \pm 3.2	5.5 \pm 3.5	2.8 \pm 1.38
Diabetic Diagnosis (%)	21 (4.6)	14 (4.7)	7 (4.3)
Current or Former Smoker (%)	278 (61.4)	199 (68.2)	79 (49.1)
Comprehensive Smoking Index ^a (mean \pm SD)	1.1 \pm 1.4	1.3 \pm 1.4	0.9 \pm 1.2
Heavy Alcohol Use (%)	91 (20.6)	61 (21.4)	30 (19.1)
Body Mass Index (mean \pm SD)	26.3 \pm 3.0	26.2 \pm 2.9	26.3 \pm 3.1

Abbreviations: MBLS, mean bone loss score; SD, standard deviation

^aContinuous measure of cumulative smoking exposure as a function of intensity, duration and time since cessation, calculated utilizing the half-life of the smoking exposure on the risk of periodontitis.

Table 2. Overall Incidence of Coronary Heart Disease and by Age at Onset of Periodontitis Among Men With Periodontitis

MBLS Change	Mean MBLS	CHD Events	Person-years	Crude IR ^c	Age at Onset ^b											
					Overall		Adjusted Overall ^a		>50 years				≤50 years			
					IRR (95% CI)	IRD ^c (95% CI)	IRR (95% CI)	IRD ^c (95% CI)	CHD Events	Person-years	IRR (95% CI)	IRD ^c (95% CI)	CHD Events	Person-years	IRR (95% CI)	IRD ^c (95% CI)
0	0.76	16	2036	0.79	1.0	0	1.0	0	10	966	1.0	0	6	1070	1.00	0
					(Ref)	(Ref)	(Ref)	(Ref)			(Ref)	(Ref)			(Ref)	(Ref)
>0-≤0.25	0.97	17	1714	0.99	1.3	0.20	1.2	.020	9	825	1.1	0.056	8	889	1.6	0.34
					(0.6, 2.5)	(-0.40, 0.82)	(0.6, 2.5)	(-0.41, 0.81)			(0.4, 2.6)	(-0.90, 1.0)			(0.6, 4.6)	(-0.43, 1.1)
>0.25-≤0.5	1.17	22	1304	1.7	2.2	.090	2.1	0.90	9	624	1.4	0.41	13	680	3.4	1.4
					(1.1, 4.1)	(0.10, 1.7)	(1.1, 3.9)	(0.10, 1.7)			(0.6, 3.4)	(-0.73, 1.6)			(1.3, 9.0)	(0.22, 2.5)
>0.5	1.62	25	957	2.6	3.3	1.8	3.3	1.8	8	383	2.0	1.1	17	574	5.3	2.4
					(1.8, 6.2)	(0.73, 2.9)	(1.8, 6.2)	(1.6, 3.6)			(0.8, 5.1)	(-0.53, 2.6)			(2.1, 13)	(0.92, 3.9)

Abbreviations: CHD, Coronary Heart Disease; CI, confidence interval; IR, incidence rate; IRD, incidence rate difference; IRR, incidence rate ratio; MBLS, mean bone loss score

^a Adjusted for smoking status

^b Unadjusted stratified estimates

^c Rates per 100 person-years

Table 3. Unadjusted Incidence of Coronary Heart Disease Among Men by Periodontitis Status at Entry

Change in MBLS	Prevalent Periodontitis							Incident Periodontitis						
	Mean MBLS	No. Teeth	CHD Events	Person-years	IR ^a	IRR (95% CI)	IRD ^a (95% CI)	Mean MBLS	No. Teeth	CHD Events	Person-years	IR ^a	IRR (95% CI)	IRD ^a (95% CI)
0	0.92	18.4	13	1177	1.1	1.0 (Ref)	0 (Ref)	0.63	19.8	3	859	0.35	1.0 (Ref)	0 (Ref)
>0-≤0.25	1.03	18.2	13	1109	1.2	1.1 (0.5, 2.3)	0.068 (-0.81, 0.94)	0.83	19.4	4	606	0.66	1.9 (0.4, 8.5)	0.31 (-0.45, 1.1)
>0.25-≤0.5	1.26	17.8	15	869	1.7	1.6 (0.7, 3.3)	0.62 (-0.44, 1.7)	0.98	19.6	7	435	1.6	4.6 (1.2, 17.8)	1.3 (0.004, 2.5)
>0.5	1.72	16.2	18	662	2.7	2.46 (1.2, 5.0)	1.6 (0.22, 3.0)	1.38	18.3	7	295	2.4	6.8 (1.8, 26.3)	2.0 (0.22, 3.8)

Abbreviations: CHD, Coronary Heart Disease; CI, confidence interval; IR, incidence rate; IRR, incidence rate ratio; IRD, incidence rate difference; MBLS, mean bone loss score

^a Rates per 100 person-years

Table 4. Adjusted Incidence of Coronary Heart Disease and by Age at Onset of Periodontitis Among Men With Incident Periodontitis

Change in MBLS	IRR ^a (95% CI)	IRD ^{a,c} (95% CI)	IRR ^b (95% CI)	IRD ^c (95% CI)	Age at Onset ^a							
					>50 years				≤50 years			
					CHD Events	Person-years	IRR (95% CI)	IRD ^c (95% CI)	CHD Events	Person-years	IRR (95% CI)	IRD ^c (95% CI)
0	1.0 (Ref)	0 (Ref)	1.0 (Ref)	0 (Ref)	1	479	1.0 (Ref)	0 (Ref)	2	380	1.0 (Ref)	0 (Ref)
>0-≤0.25	1.5 (0.34, 6.69)	0.23 (-0.54, 1.0)	1.9 (0.42, 8.9)	0.35 (-0.44, 1.1)	2	382	2.5 (0.23, 28)	0.32 (-0.52, 1.1)	2	224	1.7 (0.24, 12)	0.37 (-1.1, 1.8)
>0.25-≤0.5	3.3 (0.86, 12.9)	1.2 (-0.14, 2.5)	3.3 (0.79, 14)	1.3 (-0.19, 2.7)	4	227	8.4 (0.94, 76)	1.5 (-0.22, 3.3)	3	208	2.7 (0.46, 16)	0.92 (-0.87, 2.7)
>0.5	5.7 (1.47, 22.0)	2.0 (0.15, 3.7)	5.4 (1.4, 21)	1.9 (0.11, 3.7)	2	140	6.8 (0.62, 75)	1.2 (-0.8, 3.2)	5	155	6.1 (1.2, 32)	2.7 (-0.22, 5.6)

Abbreviations: CI, confidence interval; IRD, Incidence Rate Difference; IRR, Incidence Rate Ratio; MBLS, mean bone loss score; CHD, Coronary Heart Disease

^a Adjusted for smoking status

^b Adjusted for smoking and subject age

^c Rates per 100 person-years

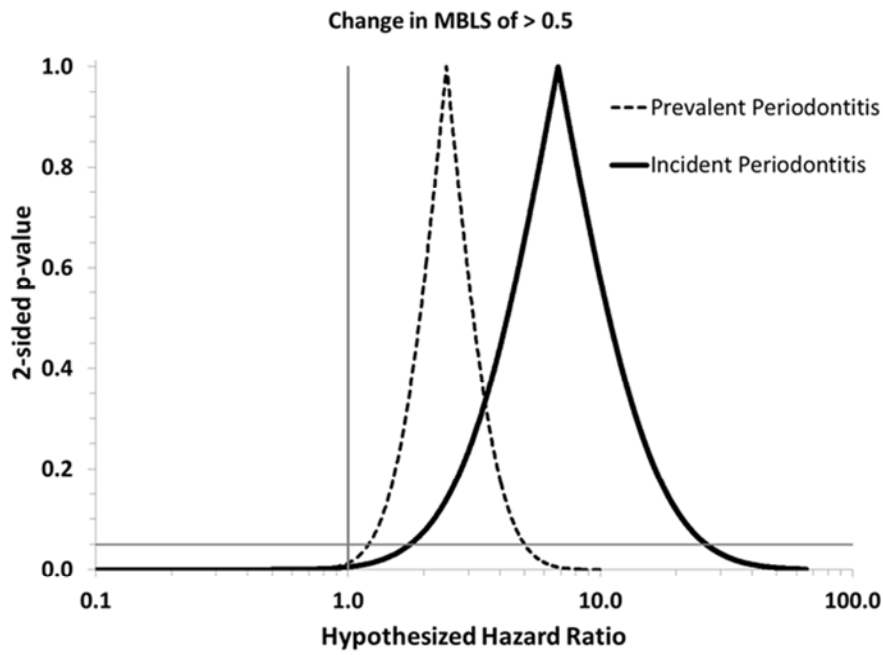


Figure 1. P-value functions for the estimated association of change in MBLs of >0.5 and incident CHD among men with prevalent and incident periodontitis.

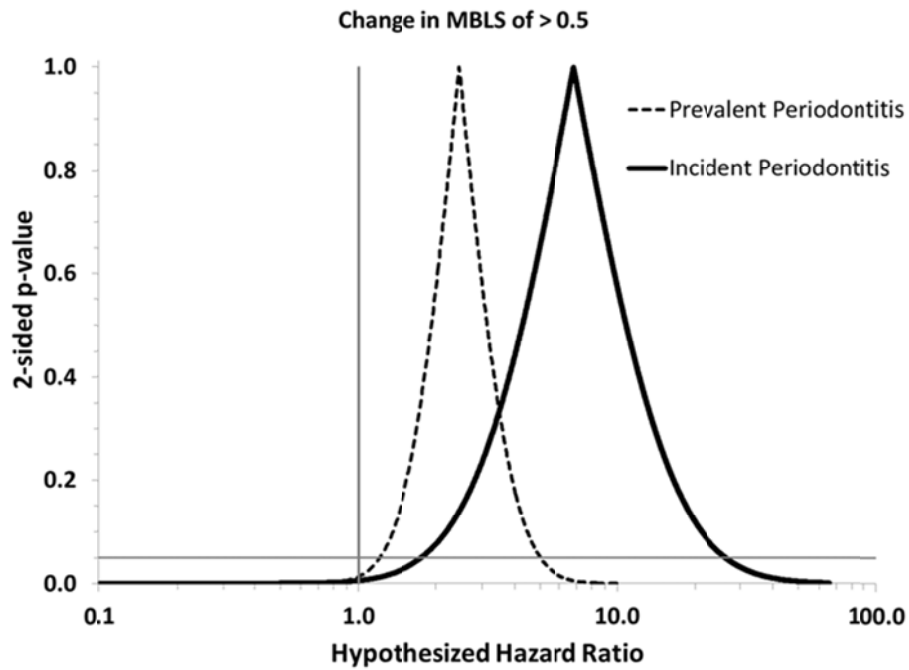


Figure 1. P-value functions for the estimated association of change in MBLs of >0.5 and incident CHD among men with prevalent and incident periodontitis.