



## Original article

# 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 subcohorts.

**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 (incident rate ratio for MBLS change >0.5 = 5.4), compared with prevalent cases (incident rate ratio for MBLS change >0.5 = 2.5).

**Conclusions:** Studying prevalent cases of periodontitis underestimates the association between incidence periodontitis and CHD.

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## 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 breakdown 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 to 54 years 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]. Noncausal pathways have included discussions of a potential genetic proinflammatory susceptibility that increases the risk of both conditions [4,5].

Because the initial work conducted in the 1980s 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].

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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 alveolar bone loss, 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, 2280 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, 1231 NAS participants volunteered to enroll in its dental component [20]. Of these, 127 never returned after baseline and 63 were edentulous, leaving 1104 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 the 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  $\geq 2$ ). 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 examination 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 years or after age 60 years ( $n = 209$ ). 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 examinations 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 0 to 5, with 0 indicating no bone loss.

Progression was characterized at each follow-up examination 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 MBLS change: 0 (reference group), greater than 0 to 0.25 or less, greater than 0.25 to 0.5 or less, and greater than 0.5.

### *Outcome identification*

CHD events were ascertained independently as part of the NAS using the same criteria as that used in the Framingham Heart Study, defined as myocardial infarction (MI), angina pectoris, and fatal CHD [24]. MI was diagnosed based on electrocardiogram 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 *International Classification of Diseases, Eighth Revision* 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 of 126 mg/dL or more, or (3) 2-hour glucose tolerance test of 200 mg/dL or more. 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 using the exposure

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