Risk of coronary heart disease in patients with periodontitis among the middled-aged and elderly in China: a cohort study

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Abstract

Background: Convincing evidence of the periodontitis as a risk factor for coronary heart disease (CHD) is lacking due to shared risk factors, and no cohort study has investigated the association between CHD and periodontitis in Chinese populations.

Methods: This study used a prospective cohort study design. The analysis included 4591 participants aged 40 years and older (3146 men and 1445 women). The association between CHD and periodontitis was estimated using relative risk (RR) calculated using modified Poisson regression. Multiple mediation analysis was used to differentiate the relative effects (RE) from different risk factors on the effect of periodontitis on CHD.

Results: In the analysis using the imputed dataset and fully adjusted model, participants with periodontitis at baseline had 37% increased risk of CHD overall compared to those without periodontitis at baseline (RR 1.37; 95% CI 0.96–1.95). Most of the association can be explained by age, sex, history of diabetes, history of hypertension, uric acid and education (RE 0.76; 95% CI 0.41–1.02).

Conclusion: Periodontitis was weakly associated with an increased risk of CHD among the middled-aged and elderly in China. Further studies are required to identify more mediators and elucidate the mechanisms of how periodontitis increases the risk of CHD.

Keywords: Periodontitis, Coronary heart disease, Oral health, Cohort study

Background

Periodontitis is an inflammatory disease that affect the supporting structures of the teeth, which could lead to tooth loss and contribute to systemic inflammation [1]. Bacteremia and systemic inflammatory caused by periodontitis are important factors in the initiation of the endothelial lesion as well as in the potentiation of the vascular wall inflammatory process that lead to the development of atherosclerosis causally [2]. Chronic infections due to periodontitis is one of the most common chronic infections have been implicated in the pathogenesis of atherosclerosis [3].

Although periodontitis as a risk factor for CHD is plausible biologically, convincing evidence is lacking [4–6]. It is difficult to interpret the association due to common risk factors such as diabetes and smoking are shared between CHD and periodontitis [7, 8].

According to the China’s Fourth National Oral Health Epidemiological Survey of 2017 [9], periodontal health condition becomes increasingly worse among the
middled-aged and elderly in China. Meanwhile, CHD is the second leading cause of cardiovascular death in the Chinese population [10]. Unfortunately, there were no cohort studies estimating the association between CHD and periodontitis in Chinese populations. We aimed to speculate whether periodontitis is a direct risk factor for CHD among the middled-aged and elderly in China and quantify mediation/confounding effects due to shared factors.

Methods
Study design and participants
The Beijing health management cohort (BHMC) is a large prospective dynamic cohort study established in 2008 in Beijing, China. The BHMC study was conducted based on health examination populations from the Beijing Xiaotangshan Examination Center and Beijing Physical Examination Center. The recruited participants were asked to take an annual health examination, including physical examination (height, weight, blood pressures), face-to-face questionnaire survey (demographic variables, lifestyles, diseases history) and biochemical examination. BHMC was designed to investigate the risk factors and biomarkers for metabolism-related diseases. Details of the study design have been described previously [11]. In this study, we used a prospective cohort study design. This longitudinal cohort consisted of 6550 participants aged 40 years and older attended health check-ups in 2014 at baseline and 2019 at follow-up. We first excluded 1479 participants without oral examinations in baseline or internal medicine examinations, and then we excluded 480 participants with history of CHD, stroke, cancer or rheumatoid arthritis in baseline. The remaining 4591 participants were enrolled in final analysis. The flowchart of the study is summarized in Fig. 1.

Data collection and definitions
Questionnaire interviews and anthropometric and laboratory measurements were performed at baseline and follow-up with the consent of all participants. The demographic characteristics and lifestyle information were collected via a standard questionnaire by our trained staff, including age, sex, education, smoking and drinking status. Smoking and drinking status were defined as ‘current’ and ‘never or former’. Education was defined as ‘below high school’ and ‘high school or above’. Physical activity was classified as ‘Moderate or higher’ (> 80 min per week) and ‘None or mild’ (< 80 min per week or none).

History of diabetes, hypertension, and periodontitis, the physical and biochemical examination data at
baseline collected from the electronic medical record system. Periodontitis cases were defined as having a probing pocket depth greater than 3 mm, with probing bleeding, clinical attachment loss, and absorption of alveolar bone. Diabetes was defined as fasting serum glucose level ≥ 7.0 mmol/L, random serum glucose level ≥ 11.1 mmol/L, or use of antidiabetic medication. Hypertension was defined as a resting blood pressure exceeding 140/90 mmHg or the use of blood pressure lowering medication. Incident cases of CHD were defined as either (1) myocardial infarction or (2) angina pectoris, or (3) silent myocardial ischemia, or (4) ischemic cardiomyopathy in the follow-up medical record. All examinations were performed by physicians.

Body mass index (BMI) was calculated as weight (in kilograms)/height^2 (in metres squared). Blood samples were collected from participants after an overnight fast of at least 12 h. Fasting laboratory measurements included uric acid (UA), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-c), high-density lipoprotein (HDL-c), creatinine (CREA), glutamic-pyruvic transaminase (ALT), glutamic-oxalacetic transaminase (AST), globulin (GLB), C-reactive protein (CRP), hemoglobin (HGB), and total protein (TP). Blood samples were measured by enzymatic method using a chemistry analyzer (Beckman LX 20, America) at the central laboratory of the hospital.

Statistical analyses

Data were presented as mean (standard deviation) for continuous variables. Categorical variable was described as number. We used the Wilcoxon signed-rank test (for continuous variables), or the Chi-squared test (for categorical variables) to investigate differences in characteristics at baseline between participants with periodontitis and without periodontitis.

The association between CHD and periodontitis was estimated using relative risk (RR) calculated using modified Poisson regression [12]. All potential confounding variables in the current regression analyses were collected at baseline. Model 1 was adjusted for age and sex. Then, Model 2 was adjusted for age, sex, BMI and history of diabetes. Model 3 was adjusted for UA, TG, TC, CREA, GLB, TP, ALT, AST, and HGB additionally. Lastly, based on Model3, Model 4 was adjusted for education, smoking, drinking, and physical activity. To reduce potential bias caused by including only participants with complete information and exploit the information in incomplete record participants, we used the multiple imputation implemented in the R package Mice [13] to get robust estimates. Missing values are provided in Table S1 (Additional file 1).

We used multiple mediation analysis implanted by the mma package [14] to differentiate the relative effects (RE) from different risk factors on the effect of periodontitis on CHD. Mediation analysis refers to the statistical techniques attempting to make inferences on mediation/confounding effects (effects from X to Y through different paths) [15]. Direct effect of periodontitis is interpreted as the remaining outcome disparity if distributions of various risk factors across periodontitis and non-periodontitis groups could be equalized. The indirect effect (IE) from a certain risk factor (mediator/confounder) is the change in the outcome disparity if the distributions of the risk factor can be set as the same across periodontitis and non-periodontitis groups, while distributions for other risk factors are kept as observed. RE is defined as the ratio of the indirect or direct effect over the total effect. We used the multivariate additive regression trees (MART) to fit variable relationships.

The mma package also provides generic functions to help identify the mediators/confounders and covariate. It tested the significance of two associations: (1) between periodontitis and the potential mediator/confounder; and (2) between the potential mediator/confounder and CHD, when other variables are controlled. For this selection process, we set the significance level at 0.25 to reduce the risk of falsely ignoring important variables. The confidence intervals were calculated based on 200 bootstrap samples. All analyses were performed using R Studio Version 1.1.423. \( p < 0.05 \) (2-sided) was considered statistically significant.

Results

The final analysis included 4591 individuals. Average age at baseline was 53.9 years. During the follow-up period, 133 participants were diagnosed with CHD. At baseline, 1268 (27.6%) participants were diagnosed with periodontitis. During the follow-up period, 55 patients developed CHD from among those with periodontitis. In the non-periodontitis group, CHD occurred in 78 patients. A significant association was seen between periodontitis at baseline and incident CHD \( (p < 0.001) \). The detailed information of the baseline characteristics was presented in Table 1.

The adjusted RRs and 95% CIs of periodontitis for the risk of CHD are shown in Table 2. Periodontitis was weakly associated with the risk of CHD when adjusted for age and sex \( (RR \ 1.35; \ 95\% \ CI \ 0.95–1.91) \). In Model 2 and Model 3, periodontitis was weakly associated with an increased risk of CHD before multiple imputation in the participants with incomplete data, although the association were not statistically significant. In the analysis using the imputed dataset and fully adjusted model, we observed that periodontitis was weakly associated...
with the risk of CHD overall \((p=0.07)\). Participants with periodontitis at baseline had 37% increased risk of CHD overall compared to those without periodontitis at baseline \((RR 1.37; 95\% \text{ CI } 0.96–1.95)\).

The test results and identified potential mediators/confounders was shown in Table S2 (Additional file 1). Age, sex, history of diabetes, history of hypertension, UA, and education were chosen as potential mediator/confounder. Figure 2 shows the RE for the CHD from the MART model. If the “Age” could be set equivalent among participants with and without periodontitis, the effect of periodontitis on CHD would reduce by 49%. Other variables such as sex (8%), history of diabetes (6%), and history of hypertension (6%) also significantly explain the association. An interesting variable is education, which have a negative relative effect \((-2\%)\) (opposite to the total

### Table 1 Baseline characteristics of the study population

| Variable          | Total \((N = 4591)\) | Without periodontitis \((N = 3323)\) | With Periodontitis \((N = 1268)\) | \(p\) Value* |
|-------------------|----------------------|-------------------------------------|---------------------------------|-------------|
| Age(year)         | 53.9(11)             | 52.8(10.8)                          | 56.9(10.9)                      | <0.001      |
| Sex               |                      |                                     |                                 |             |
| Men               | 3146                 | 2125                                | 1021                            | <0.001      |
| Women             | 1445                 | 1198                                | 247                             |             |
| BMI               | 25.5(3.2)            | 25.4(3.2)                           | 25.8(3.2)                       | <0.001      |
| Education level   |                      |                                     |                                 |             |
| Below high school | 248                  | 163                                 | 85                              | 0.024       |
| High school or above | 2133               | 1552                                | 581                             |             |
| Current smoking   |                      |                                     |                                 |             |
| Yes               | 752                  | 522                                 | 230                             | 0.033       |
| No                | 1506                 | 1111                                | 395                             |             |
| Current drinking  |                      |                                     |                                 |             |
| Yes               | 1285                 | 909                                 | 376                             | 0.09        |
| No                | 901                  | 668                                 | 233                             |             |
| Physical activity |                      |                                     |                                 |             |
| None or mild      | 1048                 | 760                                 | 288                             | 0.98        |
| Moderate or higher | 1134                | 824                                 | 310                             |             |
| Hypertension      |                      |                                     |                                 |             |
| Yes               | 1816                 | 1249                                | 567                             | <0.001      |
| No                | 2775                 | 2074                                | 701                             |             |
| Diabetes          |                      |                                     |                                 |             |
| Yes               | 426                  | 260                                 | 166                             | <0.001      |
| No                | 4165                 | 3063                                | 1102                            |             |
| TG (mmol/L)       | 1.6(1.3)             | 1.6(1.3)                            | 1.7(1.4)                        | <0.001      |
| TC (mmol/L)       | 4.8(0.9)             | 4.8(0.9)                            | 4.8(0.9)                        | 0.45        |
| HDL-c (mmol/L)    | 1.3(0.3)             | 1.3(0.4)                            | 1.3(0.3)                        | <0.001      |
| LDL-c (mmol/L)    | 3.1(0.8)             | 3.1(0.8)                            | 3.1(0.8)                        | 0.90        |
| UA (µmol/L)       | 344.1(85.8)          | 340.7(86.4)                         | 353.0(83.6)                     | <0.001      |
| GLB (g/L)         | 26.4(3.4)            | 26.3(3.4)                           | 26.5(3.3)                       | 0.051       |
| CREA (µmol/L)     | 75.8(16.1)           | 74.8(15.3)                          | 78.3(17.9)                      | <0.001      |
| ALT (U/L)         | 21.1(12.2)           | 21.1(12.2)                          | 21.2(12.2)                      | 0.18        |
| AST (U/L)         | 20.1(7.0)            | 20.1(7.0)                           | 20.2(7.1)                       | 0.63        |
| CRP (mg/L)        | 1.3(2.7)             | 1.3(2.9)                            | 1.3(2.0)                        | 0.17        |
| HGB (g/L)         | 150.7(15.4)          | 149.6(15.7)                         | 153.5(14.1)                     | <0.001      |
| TP (g/L)          | 72.7(3.9)            | 72.6(3.9)                           | 72.8(3.9)                       | 0.34        |

Numerical variables were expressed as mean (SD); categorical variables were expressed as number
Abbreviations: BMI body mass index, UA uric acid, TC total cholesterol, TG triglycerides, LDL-c low-density lipoprotein, HDL-c high-density lipoprotein, CREA creatinine, ALT glutamic-pyruvic transaminase, AST glutamic-oxalacetic transaminase, GLB globulin, CRP C-reactive protein, HGB hemoglobin, TP total protein
*Wilcoxon signed-rank test (for continuous variables), or the Chi-squared test (for categorical variables)
effect), but this association were not statistically signifi-
cant (95% CI −0.10 to 0.02). All the mediators/confound-
ers explained most of the effect of periodontitis on CHD
(RE 0.76; 95% CI 0.41–1.02). The detailed results of the
multiple mediation analysis were presented in Table S3
(Additional file 1).

Fig. 2 shows the marginal effect of the significant
variables in MART model, and the distribution of the
variables in participants with and without periodontitis
at baseline, respectively. Compared with those without
periodontitis at baseline, participants with periodon-
titis at baseline have more older participants, male, and
higher prevalence of diabetes and hypertension. All those
factors were associated with an increased risk of CHD.

Discussion
The main finding of this prospective cohort study
was that periodontitis was weakly associated with an
increased risk for CHD among the middled-aged and
elderly in China. Previous epidemic studies in other
regions have shown associations between periodontitis
and CHD, and most of existing ones are biased towards
periodontitis is a risk factor for CHD [5]. However, some
studies found no significant relationship between peri-
odontitis and CHD [16–18]. This may be attributed to
differences in the target population and the definition
of periodontitis. In some studies, periodontitis was self-
reported, and then no significant results were found [16,
18]. Some studies found significant results when peri-
odontal pocket was used as a main indicator of periodon-
titis [19, 20]. Basing the Centers for Disease Control and
Prevention in partnership with the American Academy of
Periodontology case definitions [21], Niramol et al. found
a significant association between severe periodontitis
and the incidence of CHD [22]. In our study, periodontal
pocket depth greater than 3 mm is a main indicator for
periodontitis.

We noted that a stronger association was obtained
when the missing data in Model 4 were simulated. How-
ever, the result obtained from original data was not sig-
nificant. The likely reason for this is that the participants
who completed questionnaires had a degree of hetero-
geneity. In these people, 2133 participants had received
the high school or above education, and only 248 par-
ticipants had received the below high school education.
When we fitted model adjusted only for age and sex using
this data, the result was not significant (RR 1.25; 95% CI
0.78–1.99). After applying multiple imputation, potential
bias caused by including only participants with complete
information were minimized.

We observed that age, sex, history of diabetes, and
history of hypertension have a significant indirect
effect in explaining the effect of periodontitis on CHD.
Almost half of the effect of periodontitis on CHD that
can be explained by age. It should be noted that the
age is reported in years, which means age may explain
more disparity for this association. For sex, previous
studies identified that men disproportionately develop
periodontal diseases due to a combination of biologi-
cal and gender related reasons including immune sys-
tem factors, hormone differences, poorer oral hygiene
behaviors, and greater tobacco use [23]. Compared
with women, men also reported a significantly higher
prevalence of CHD [24, 25]. For diabetes, some epi-
demiological studies and reviews have reported that

### Table 2 Results of modified passion regression model for
periodontitis and CHD with their relative risks (RRs) and 95%
confidence intervals (CIs)

| Model | N* | RR (95%CI) | p Value | Model | N* | RR (95%CI) | p Value |
|-------|----|-----------|---------|-------|----|-----------|---------|
| 1     | 4591| 1.35(0.95,1.91) | 0.08 | – | – | – | – |
| 2     | 4357| 1.34(0.93,1.90) | 0.10 | 1.31(0.92,1.85) | 0.12 | – | – |
| 3     | 3208| 1.34(0.89,2.00) | 0.15 | 1.32(0.93,1.86) | 0.11 | – | – |
| 4     | 1651| 1.19(0.72,1.97) | 0.49 | 1.37(0.96,1.95) | 0.07 | – | – |

Model 1 adjusted for age and sex
Model 2 model 1 and BMI and history of diabetes
Model 3 model 2 and uric acid (UA), total cholesterol (TC), triglycerides (TG), creatinine (CREA), glutamic-pyruvic transaminase (ALT), glutamic-oxalacetic transaminase (AST), globulin (GLB), hemoglobin (HGB), and total protein (TP)
Model 4 model 3 and education, smoking, drinking, and physical activity

*The number of participants with the complete information for models

**Fig. 2** Estimated relative effects (RE) on the effect of periodontitis on CHD from the multiple mediation analysis. RE is defined as the ratio of the indirect effect of different risk factors on the total effect of periodontitis on CHD. DE represents the ratio of the direct effect of periodontitis on the total effect of periodontitis on CHD. Abbreviations: DE direct effect, UA uric acid
Periodontitis is a potential risk factor for diabetes mellitus. In fact, early blood glucose fluctuations are thought to be associated with development of poor oral health [26]; There may be a bidirectional association between oral health and type 2 diabetes [27]. Meanwhile, most patients who have type 2 diabetes mellitus develop vascular complications [28]. For hypertension, the occurrence of periodontitis leads to an increase in blood pressure [29]. Periodontitis can also lead to ineffectiveness of antihypertensive [30, 31]. Hypertension is also a risk factor for CHD among middle to old age [32, 33].

In addition, we also found UA is a potential mediator. Epidemiology studies suggested that UA levels were positively associated with periodontitis [34, 35]. Porphyromonas gingivalis is a major periodontopathogen, and its gingipain proteases play a critical role in the pathogenesis of periodontitis. Gingipain-induced UA can mediate inflammation in periodontal tissue cells [36]. UA is also associated with the risk of incident
CHD [37]. The role of UA in the link between periodontitis and CHD requires further study.

To the best of our knowledge, this is the first cohort study investigation of the association between periodontitis and CHD among the middled-aged and elderly in China, and we first used multiple mediation analysis to quantify the relative effects from different risk factors on the effect of periodontitis on CHD. This study will enhance our understanding of the association between CHD and periodontitis, and provide epidemiologic evidence in Chinese population. However, this study has some limitations. First, oxidative stress [38] and genetic factors [39, 40] may also mediate the association. We did not collect relevant variables. Second, we did not distinguish the severity of periodontitis. Third, among those who completed the questionnaire, better-educated people were vastly outnumbered by less educated people. Moreover, the observed associations of this single-center study needed further validation in other cohorts.

Conclusion

In summary, periodontitis was weakly associated with an increased risk of CHD among the middled-aged and elderly in China. However, most of the association can be explained by age, sex, history of diabetes, history of hypertension, UA and education. Further studies are required to identify more mediators and elucidate the mechanisms of how periodontitis increases the risk of CHD.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12903-021-01951-z.

Additional file 1. Summary of missing values, potential mediators/ confounders and covariates, summary of mediation/confounding effect estimations for periodontitis in CHD, and baseline characteristics of the study population categorized by CHD event.

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Authors’ contributions

KG and SW conceptualized the study.ZW, YL, LT, XY, JZ, and XG were involved in the design of the study. KG drafted the manuscript. All authors have reviewed, commented on and approved the final version of the manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The research was approved by the Ethics Committee of Capital Medical University (NO. 2013SY26) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the participating subjects prior to data collection.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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