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Periodontal disease is associated with increased coronary heart disease risk: A meta-analysis based on 38 case-control studies

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Abstract

AIM: To investigate whether periodontal disease (PD) is associated with increasing coronary heart disease (CHD) risk by performing a meta-analysis.

METHODS: Two authors independently searched PubMed and China National Knowledge Infrastructure up to January 10th, 2013 for relevant case-control studies that investigated the association between PD and CHD. After quality assessment using Newcastle-Ottawa Scale and data extraction by two independent authors, the overall and subgroup meta-analyses were performed and publication bias were examined using the Comprehensive Meta-Analysis V2 software. Potential publication bias was assessed using visual inspection of the funnel plots, Egger linear regression test, and trims and fill method.

RESULTS: Finally 38 relevant case-control studies were identified, involving 4950 CHD patients and 5490 controls. Eleven studies were rated low quality and 27 were high quality. Based on random-effects, a significant association was identified between PD and CHD (OR 3.79, 95%CI: 2.23-6.43, $P < 0.001$, $I^2 = 98.59\%$), and sensitivity analysis showed that this result was robust. Subgroup analyses according to adjusted/unadjusted ORs, source of control, methodological quality, end point, assessment of PD/CHD, and ethnicity also indicated a significant association. Publication bias was detected, and the estimated OR including the "missing" studies did not substantially differ from our estimate with adjustment for missing studies (OR 4.15, 95%CI: 2.62-6.54, $P < 0.001$).

CONCLUSION: Based on the meta-analysis, PD is probably associated with CHD risk independently and significantly.

Key words: Periodontal disease; Coronary heart disease; Case-control study; Risk factor; Meta-analysis

Core tip: Growing evidence indicated that periodontal disease (PD) might be associated with coronary heart disease (CHD), however, results from the studies were inconsistent. This meta-analysis based on 38 case-control studies indicated that PD increased a 3.79-fold risk of CHD (OR = 3.79, 95%CI: 2.23-6.43, $P < 0.001$, $I^2 = 98.59\%$). The results showed that PD is probably an independent and significant risk factor for CHD.

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INTRODUCTION

Coronary heart disease (CHD) is one of the major causes of mortality, account for nearly 30% of deaths worldwide[1]. As almost half of all first onset of CHD events occur in asymptomatic patients[2], it is important to seek CHD risk factors and accurately identify high-risk individuals and guide the risk reduction interventions, prevention, and lifestyle changes. CHD is a complex disease, epidemiologic studies have suggested that the etiology of CHD involved interactions of genetics, environmental factors, and gene-gene and gene-environment[3]. Environmental factors (including psychological and social factors)[4,5] are the classical risk factors for CHD, however, these markers do not explain the etiology of CHD to the fullest of its extent. Given the importance of fatal health problem related to CHD, efforts are being made to identify other modifiable risk factors that play a role in the etiology of CHD.

Periodontal disease (PD) is a group of inflammatory diseases which affect the supporting tissues of the tooth, approximately at least 35% dentate adults aged 30-90 years in United States suffer from PD[6], and it also affects up to 90% of the worldwide population[7]. Based on the theory of "focal infection" which emerged at the beginning of the 20th century, many studies have observed a possible role of PD as a risk factor for systemic conditions over the past two decades[8], such as cardiovascular diseases[9], diabetes[10], and chronic obstructive pulmonary disease[11].

Growing evidences indicated that chronic infections and inflammation (such as PD) might play a role in the initiation and progression of CHD[12]. Many epidemiological studies have investigated the link between PD and risk of CHD, and most of them found a positive association, even though some results are varied or even contradictory among studies. There was a published meta-analysis based on 8 cross sectional and 14 case-control studies by Blaizot *et al*[9] in 2009, which identified that there were higher odds of developing CHD in patients with PD (OR 2.35, 95%CI: 1.87-2.96, $P < 0.0001$). However, this meta-analysis did not perform subgroup analyses because of the study design, and adjusted or unadjusted factors. As we know, a cross sectional design is subjected to more confounding and biases than a case-control design, and adjusted data could obtain more precise point estimate than unadjusted data. Up to now, there have been 38 case-control studies[13-50] published in English or Chinese.

An improved understanding of this association may have important public health and clinical implications, for prevention and treatment of PD would reduce the CHD events. This meta-analysis aims to (1) evaluate the inconsistent results from published case-control studies on the association between PD and risk of CHD; (2) gain a more precise estimate association; and (3) provide a general interpretation of the results in the context of other evidences and propose suggestions for the prevention and treatment of the diseases.

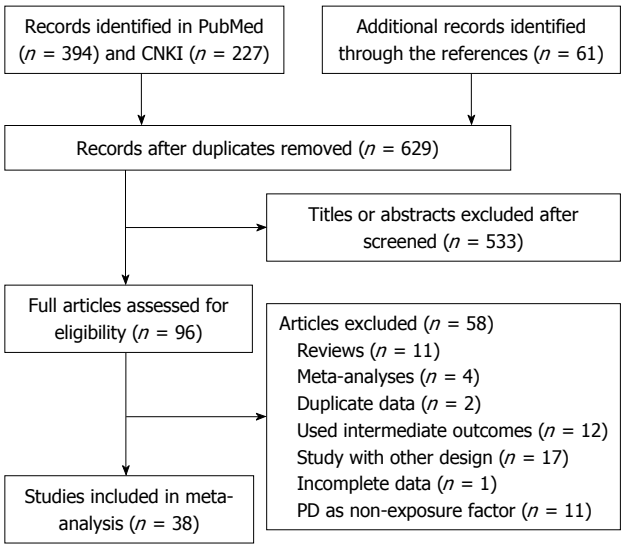

Figure 1 Flow chart of included case-control studies that tested the association between periodontal disease and risk of coronary heart disease. PD: Periodontal disease; CHD: Coronary heart disease; CNKI: China National Knowledge Infrastructure.

MATERIALS AND METHODS

We followed the proposed MOOSE (Meta-Analysis of Observational Studies in Epidemiology)[51] guidelines to report the present meta-analysis.

Literature search

We initially identified published studies that investigated the association between PD and CHD by searching the PubMed and China National Knowledge Infrastructure databases up to January 10th, 2013. The following search terms were used: (1) "PD" or "peridontal disease" or "periodontitis" or "periodontal attachment loss" or "periodontal pocket" or "alveolar bone loss", and (2) "CHD" or "coronary artery disease" or "myocardial infarction (MI)" or "angina pectoris" or "ischemic heart disease". The studies were published in either English or Chinese. We also reviewed the reference lists of retrieved articles, previous meta-analysis, and recent reviews.

Study selection

Any study met all of the following criteria was included: (1) the study was of a case-control design; (2) clear diagnostic criteria for PD and CHD were reported; (3) the association between PD and risk of CHD was investigated, and PD is the exposed factor; and (4) the ORs and the

Table 1 Characteristics and methodological quality of included 38 case-control studies in the meta-analysis

Ref.	Location	Sample size	Age (case/control, yr)	Source of control	Assessment		End points	OR (95%CI)	NOS
					PD	CHD			
Li *et al*[13]	China	88/128	> 60	Hospital-based	PI	C	CHD	1.85 (1.07-3.20)	4
López *et al*[14]	Chile	35/51	42.5 ± 5.7/40.5 ± 6.3	Hospital-based	PPD	ECG	CHD	3.17 (1.31-7.65)[1]	6
Huang *et al*[15]	China	146/136	58.7 ± 8.9	Hospital-based	Q	CAG	CHD	2.27 (1.40-3.68)	5
Liu *et al*[16]	China	216/216	59.4 ± 15.3/57.9 ± 13.7	Population-based	PI	CAG	CHD	5.42 (3.32-8.86)	4
Rutger Persson *et al*[17]	Sweden	80/80	63.4 ± 8.9/61.9 ± 9.1	Population-based	ABL	ECG	MI	14.1 (5.8-34.4)[1]	7
Geerts *et al*[18]	Belgium	108/62	59.2 ± 10.9/57.7 ± 8.7	Hospital-based	PPD	C	CHD	6.50 (1.80-23)[1]	7
Montebugnoli *et al*[19]	Italy	63/50	52.3 ± 4.9/54.5 ± 6.1	Population-based	PPD	CAG	CHD	4.61 (1.00-23.20)[1]	8
Renvert *et al*[20]	Sweden	88/80	62.7 ± 9.1/NA	Hospital-based	PPD	C	MI	7.67 (1.13-51.92)[1]	6
Tang *et al*[21]	China	250/250	⩾ 45	Hospital-based	CPI	C	CHD	1.95 (1.36-2.78)	4
Buhlin *et al*[22]	Sweden	143/50	65.9 ± 8.6/64.5 ± 8.3	Population-based	PPD	CAG	CHD	3.80 (1.68-8.74)[1]	8
Liu *et al*[23]	China	45/40	54.9 ± 8.1/51.2 ± 6.5	Hospital-based	PI	CAG	CHD	18.70 (6.25-55.93)	4
Wang *et al*[24]	China	216/216	59 ± 15/58 ± 14	Population-based	ABL	CAG	CHD	1.76 (1.31-2.36)[1]	7
Andriankaja *et al*[25]	United States	537/800	54.6 ± 8.5/55.0 ± 0.0	Population-based	CAL	C	MI	2.24 (1.60-3.13)[1]	8
Barilli *et al*[26]	Brazil	40/59	49.2 (30-79)	Hospital-based	CPI	C	CHD	61 (17.26-214.86)	5
Briggs *et al*[27]	United Kingdom	92/79	56.7 ± 6.3/58.2 ± 6.7	Population-based	PPD	CAG	CHD	3.06 (1.02-9.17)[1]	8
Geismar *et al*[28]	Denmark	110/140	65/62.6	Hospital-based	ABL	ECG	CHD	2.0 (0.77-5.08)[1]	7
Li *et al*[29]	China	357/305	72.5 ± 8.9	Population-based	PI	CAG	CHD	1.16 (0.91-1.48)	6
Spahr *et al*[30]	Germany	263/526	61.0 ± 7.1/61.0 ± 7.1	Population-based	CPI	CAG	CHD	1.67 (1.08-2.58)[1]	8
Zhang *et al*[31]	China	77/74	50.2 ± 9.6/50.8 ± 9.5	Population-based	PPD	CAG	CHD	2.13 (1.08-4.22)	6
Zhang *et al*[32]	China	277/238	57 ± 11.3/55 ± 10.8	Hospital-based	CAL	CAG	CHD	2.70 (1.52-4.80)[1]	7
Latronico *et al*[33]	Italy	15/19	57.7/55.1	Population-based	ABL	CAG	CHD	5.85 (1.03-33.12)	6
Nonnenmacher *et al*[34]	Germany	45/45	63.5 ± 7.4/63.6 ± 7.4	Hospital-based	CAL	CAG	CHD	3.2 (1.2-9.0)[1]	7
Rech *et al*[35]	Brazil	58/57	59.3/70	Hospital-based	PPD	ECG	MI	1.8 (0.7-4.7)[1]	6
Ge *et al*[36]	China	13/30	55.1 ± 4.8/51.2 ± 4.7	Hospital-based	CAL	CAG	CHD	2.53 (1.01-6.32)[1]	6
Meng *et al*[37]	China	150/150	71.2 ± 4.6/71.9 ± 4.7	Population-based	ABL	C	CHD	2.95 (1.74-5.02)	5
Wu *et al*[38]	China	77/75	53.81 ± 8.25/ 51.14 ± 6.44	Hospital-based	CAL	CAG	CHD	2.18 (1.52-3.13)	5
Zamirian *et al*[39]	Iran	80/80	54.0 ± 8.7/51.9 ± 9.4	Hospital-based	CAL	ECG	MI	3.18 (1.37-7.42)[1]	6
Zhu *et al*[40]	China	98/104	61.34 ± 9.63	Population-based	CAL	C	MI	11.43 (2.59-50.34)	5
Dong *et al*[41]	China	161/162	33-66/30-70	Population-based	ABL	CAG	CHD	5.74 (2.07-15.90)[1]	7
Ma *et al*[42]	China	146/257	45-72	Hospital-based	CAL	CAG	CHD	2.36 (1.49-3.73)	5
Oikarinen *et al*[43]	Kuwait	88/88	48.8 ± 10.0/47.0 ± 11.6	Hospital-based	ABL	C	CHD	19.69 (19.36-20.02)	6
Sun *et al*[44]	China	167/242	68.28 ± 10.53/ 50.18 ± 10.56	Hospital-based	CAL	CAG	CHD	9.10 (0.87-95.07)[1]	7
Willershausen *et al*[45]	Germany	125/125	61.8 ± 10.4/63.4 ± 10.7	Population-based	CAL	ECG	MI	3.65 (2.02-6.56)[1]	7
Bokhari *et al*[46]	Pakistan	45/35	41.67 ± 5.11/ 40.31 ± 6.97	Hospital-based	PPD	CAG	CHD	6.37 (1.26-32.27)	6
Chen[47]	China	46/34	38-68/35-66	Hospital-based	ABL	CAG	CHD	9.87 (3.50-27.82)	4
Sikka *et al*[48]	India	100/100	54.97 ± 7.97/ 55.1 ± 8.08	Population-based	CPI	CAG	CHD	2.66 (1.50-4.71)	7
Ashraf *et al*[49]	Pakistan	145/145	53.3 ± 12.3/51.7 ± 11.6	Hospital-based	CPI	C	CHD	1.20 (0.93-1.55)[1]	7
Zhang *et al*[50]	China	162/162	66.7/66.0	Hospital-based	Q	CAG	CHD	2.16 (1.65-2.83)[1]	6

[1]Adjusted OR and 95%CI. PD: Periodontal disease; CHD: Coronary heart disease; NOS: Newcastle-Ottawa Scale; CAG: Coronary arteriography; ECG: Electrocardiograph; MI: Myocardial infarction; CAL: Clinical attachment loss; PPD: Periodontal pocket depth; ABL: Alveolar bone loss; CPI: Community periodontal index; PI: Periodontal index; Q: Questionnaire; C: Cardiologist.

corresponding 95%CIs, or the number of events were reported. Two authors independently evaluated the eligibility of all retrieved studies; disagreements were resolved by discussion or consultation with a third author.

Methodological quality assessment

The methodological quality of included studies was assessed independently by two authors according to the Newcastle-Ottawa Scale (NOS) for case-control study[52]. The NOS for case-control study consists of 3 parameters of quality: selection, comparability, and exposure assessment. It assigns a maximum of 4 points for selection, a maximum of 2 points for comparability, and a maximum of 3 points for exposure. Therefore, 9 points is the highest score, reflecting the highest quality. We defined overall quality rating scores < 6 as low quality, and ⩾ 6 as high quality. All discrepancies between authors were addressed by a common reevaluation of the original article.

Data extraction

Two authors independently extracted data of each study using a preliminary standardized data collection form. Data extracted included: first author's last name, year of publication, country of study; characteristics of study

Table 2 Adjustments in case-control studies included in this meta-analysis

Ref.	Adjustment
López *et al*[14]	DM, systolic blood pressure, and smoking
Rutger Persson *et al*[17]	Smoking
Geerts *et al*[18]	Age, gender, smoking, DM, hypertension, hyperlipidemia, diet, and alcohol
Montebugnoli *et al*[19]	Age, smoking, DM, hypertension, high/low density lipoprotein, CRP, leukocytes, BMI, social class
Renvert *et al*[20]	Smoking
Buhlin *et al*[22]	Age, gender, smoking, DM, BMI, education, place of birth
Wang *et al*[24]	Gender, age, BMI, smoking, hypertension, DM, blood lipid, CRP, white blood count, and fibrinogen
Andriankaja *et al*[25]	Age, gender, hypertension, cholesterol, DM, and smoking
Briggs *et al*[27]	Smoking, education, alcohol, BMI, exercise, unemployment, hobby, plaque, and CRP
Geismar *et al*[28]	Gender, smoking, DM, and education
Spahr *et al*[30]	Age, sex, BMI, smoking, alcohol, DM, hypertension, hyperlipoproteinemia, education, exercise, and statin intake
Zhang *et al*[32]	Smoking, age, gender, BMI, hypertension, DM, high-density lipoproteincholesterol, total Cholesterol, total glycerin
Nonnenmacher *et al*[34]	Smoking and BMI
Rech *et al*[35]	Age, gender, smoking, DM
Ge *et al*[36]	Blood pressure and BMI
Zamirian *et al*[39]	Smoking and alcohol
Dong *et al*[41]	Smoking, age, and education
Sun *et al*[44]	Age and BMI
Willershausen *et al*[45]	Age, gender, and smoking
Ashraf *et al*[49]	Age, gender, and education
Zhang *et al*[50]	Age, gender, smoking, alcohol, hypertension, and BMI

DM: Diabetes mellitus; BMI: Body mass index; CRP: C-reactive protein.

population and age at baseline; number of participants with PD and CHD, and total number of participants, or ORs and relevant 95%CIs; end points of CHD, ascertainment of PD and CHD; and adjustment for covariates. Any disagreement was resolved by consensus. CHD was defined as MI, angina pectoris, and other ischemic heart diseases (IHD).

Statistical analysis

We pooled the results from single studies which were found to be both clinically and statistically appropriate. We computed pooled ORs and relevant 95%CIs using Comprehensive Meta-Analysis software, Version 2.2 (Biostat, Englewood, NJ, United States)[53], to generate forest plots, determine whether a statistical association between PD and CHD exists, assess the heterogeneity of the selected studies, and detect whether publication bias present. Heterogeneity was quantified using the I^2 statistic[54], with the low, moderate, and high I^2 values of 25%, 50%, and 75%, respectively[55], where I^2 value of 25% or lower indicated no evidence of heterogeneity, we used the fixed-effect model; otherwise, the random-effects model was used.

When heterogeneity existed, we performed subgroup and sensitivity analyses to explore possible explanations for the heterogeneity and examine the influence of various exclusion criteria on the overall risk estimate. We also investigated the influence of single study on the overall risk estimate by sequentially removing each study to test the robustness of the main results.

Potential publication bias was assessed by visual inspection of the funnel plots of overall outcome. The Egger linear regression test was used to examine the association between mean effect estimate and its variance[56]. In addition, to assess the effect of possible publication bias, we calculated the number of unpublished studies which may exist to negate the results, and the pooled OR adjusted for publication bias using the trim and fill method[57].

RESULTS

Study identification

Of 682 records searched initially, 38 case-control studies[13-50] were included in this meta-analysis. A detailed flowchart of the selection process is shown in Figure 1.

Characteristics and quality of studies

Table 1 presents the major characteristics and methodological quality of the 38 case-control studies. These studies focused on CHD only. Sample sizes ranged from 34 to 1337, involving 4950 CHD patients and 5490 controls subjects. Twenty-one studies[14,17-20,22,24,25,27,28,30,32,34-36,39,41,44,45,49,50] were adjusted covariates (Table 2), while there was no adjustment of the other 17 studies[13,15,16,21,23,26,29,31,33,37,38,40,42,43,46-48]. The methodological quality of 11 studies[13,15,16,21,23,26,37,38,40,42,47] according to NOS were rated low quality, and 27 were rated high quality[14,17-20,22,24,25,27-36,39,41,43-46,48-50]. All the CHD patients were confirmed and non-CHD patients were excluded by coronary arteriography (CAG), cardiologists, or electrocardiography (ECG).

PD and risk of CHD

Of all 38 studies, six studies[19,28,29,35,44,49] showed no statistical difference, and all the 38 studies identified significantly increased risk of developing CHD (OR 3.79, 95%CI: 2.23-6.43, $P < 0.001$). Substantial heterogeneity was observed ($I^2 = 98.59\%$, $P < 0.001$). Figure 2 shows the results from the random-effects model pooling the ORs and 95%CIs.

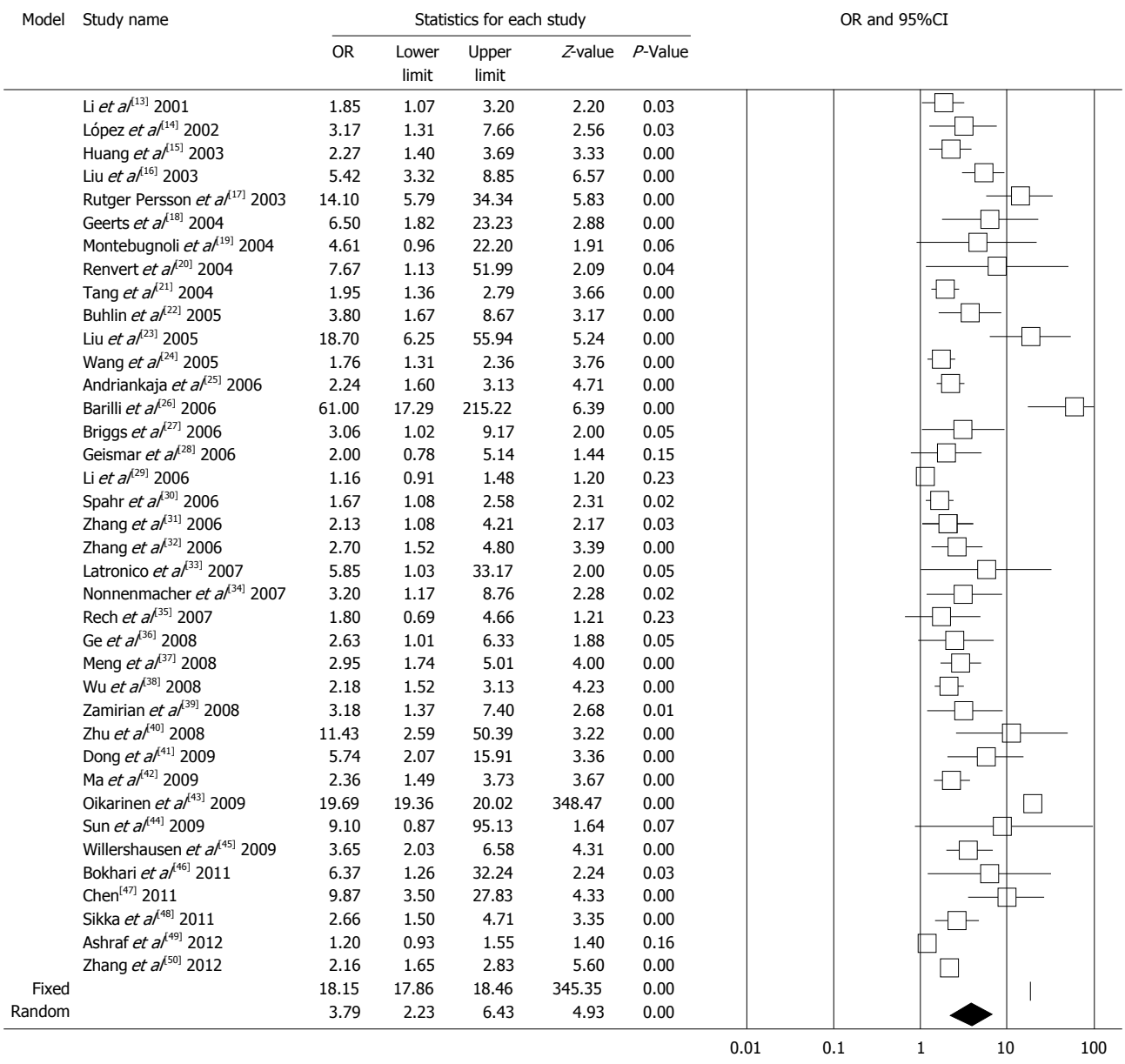

Figure 2 Forest plot of periodontal disease and risk of coronary heart disease, using pooled random-effects model. The pooled odds ratio is represented by a diamond of standard height, with the width indicating the 95%CI.

Subgroup and sensitivity analyses

Table 3 shows the results of subgroup analyses by adjustment for covariates, source of control, methodological quality, end point, assessment of PD, assessment of CHD, and ethnicity. All these analyses indicated that PD is a risk factor for CHD. Sensitivity analysis was performed by sequentially removing each study, the significance of pooled ORs was not influenced by the omission of any single study (the values of ORs were between 3.05 and 3, 91, and the relevant 95%CIs between 2.06 and 6.62), suggesting that the results of this meta-analysis were stable (Figure 3).

Publication bias

Figure 4 shows that the funnel plot was asymmetrical, indicating publication bias existed; this was also confirmed by Egger linear regression test ($P < 0.001$). As the evidence of bias could be due to inadequate statistical power, we used the non-parametric method of "trim and fill" and estimated 3 possible missing studies based on random-effects model (black spots in Figure 4). The estimated OR including the "missing" studies did not substantially differ from our estimate with adjustment for missing studies (OR 4.15, 95%CI: 2.62-6.54, $P < 0.001$).

DISCUSSION

In 1989, Mattila *et al*[58] reported that dental health was significantly associated with acute MI, and this association remained valid after adjustment for age, social class, smoking, serum lipid concentrations, and the presence of diabetes. Since then, many observational studies have emerged to investigate the relationship between

Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	*Z*-value	*P*-value
Li *et al*[13] 2001	3.86	2.26	6.61	4.93	0.00
López *et al*[14] 2002	3.80	2.22	6.51	4.87	0.00
Huang *et al*[15] 2003	3.84	2.24	6.58	4.90	0.00
Liu *et al*[16] 2003	3.75	2.18	6.45	4.77	0.00
Rutger Persson *et al*[17] 2003	3.65	2.13	6.26	4.71	0.00
Geerts *et al*[18] 2004	3.74	2.18	6.39	4.81	0.00
Montebugnoli *et al*[19] 2004	3.77	2.20	6.44	4.85	0.00
Renvert *et al*[20] 2004	3.73	2.18	4.37	4.82	0.00
Tang *et al*[21] 2004	3.86	2.26	6.60	4.93	0.00
Buhlin *et al*[22] 2005	3.79	2.21	6.40	4.85	0.00
Liu *et al*[23] 2005	3.63	2.12	6.22	4.70	0.00
Wang *et al*[24] 2005	3.87	2.27	6.61	4.96	0.00
Andriankaja *et al*[25] 2006	3.85	2.24	6.59	4.90	0.00
Barilli *et al*[26] 2006	3.53	2.06	6.04	4.60	0.00
Briggs *et al*[27] 2006	3.61	2.23	6.52	4.88	0.00
Geismar *et al*[28] 2006	3.85	2.25	6.59	4.92	0.00
Li *et al*[29] 2006	3.91	2.33	6.56	5.16	0.00
Spahr *et al*[30] 2006	3.88	2.27	6.62	4.96	0.00
Zhang *et al*[31] 2006	3.85	2.25	6.59	4.91	0.00
Zhang *et al*[32] 2006	3.82	2.23	6.55	4.88	0.00
Latronico *et al*[33] 2007	3.75	2.19	6.41	4.83	0.00
Nonnenmacher *et al*[34] 2007	3.80	2.22	6.51	4.87	0.00
Rech *et al*[35] 2007	3.86	2.26	6.61	4.94	0.00
Ge *et al*[36] 2008	3.83	2.24	6.55	4.90	0.00
Meng *et al*[37] 2008	3.81	2.22	6.54	4.86	0.00
Wu *et al*[38] 2008	3.85	2.25	6.59	4.90	0.00
Zamirian *et al*[39] 2008	3.80	2.22	6.52	4.87	0.00
Zhu *et al*[40] 2008	3.69	2.16	6.31	4.76	0.00
Dong *et al*[41] 2009	3.74	2.19	6.41	4.81	0.00
Ma *et al*[42] 2009	3.84	2.24	6.58	4.89	0.00
Oikarinen *et al*[43] 2009	3.05	2.48	3.75	10.52	0.00
Sun *et al*[44] 2009	3.72	2.18	6.36	4.82	0.00
Willershausen *et al*[45] 2009	3.79	2.21	6.50	4.84	0.00
Bokhari *et al*[46] 2011	3.74	2.19	6.40	4.82	0.00
Chen[47] 2011	3.69	2.15	6.32	4.76	0.00
Sikka *et al*[48] 2011	3.82	2.23	6.55	4.88	0.00
Ashraf *et al*[49] 2012	3.91	2.32	6.58	5.12	0.00
Zhang *et al*[50] 2012	3.85	2.24	6.60	4.90	0.00
	3.79	2.23	6.43	4.93	0.00

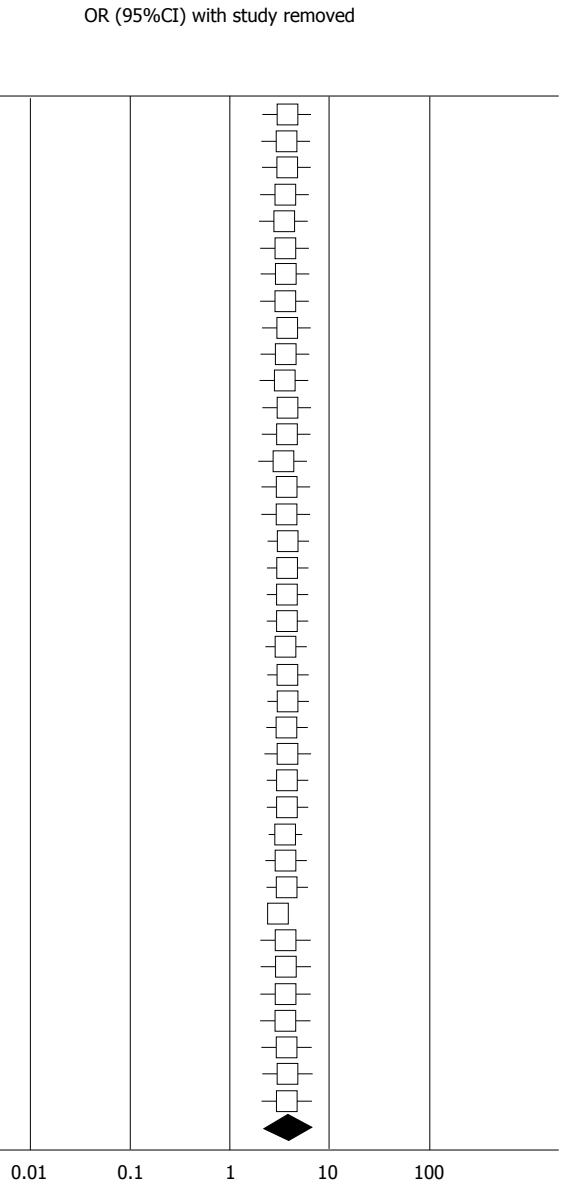

Figure 3 Forest plot of sensitivity analysis by removing each study in each turn. The pooled odds ratio is represented by a diamond of standard height, with the width indicating the 95%CI.

oral health and CHD, and PD was of special concern. However, the result remains controversial. In the present study, we performed a meta-analysis about the association between PD and CHD risk based on 38 case-control studies, and identified that subjects with PD had higher odds and higher risk of developing CHD than subjects without PD. Subgroup analyses based on adjustment for covariates, source of control, methodological quality, end point, assessment of PD, assessment of CHD, and ethnicity yielded significant and consistent results.

Compared with the previous meta-analysis by Blaizot *et al*[9] in 2009, whose result based on pooled 8 cross-sectional and 14 case-control studies identified 2.35 times higher risk of developing CHD in patients with PD (OR 2.35, 95%CI: 1.87-2.96, $P < 0.001$), our meta-analysis identified the higher risk (OR 3.79, 95%CI: 2.23-6.43, $P < 0.001$) based on 38 case-control studies. Obviously, our meta-analysis separated case-control studies from cross-sectional studies, therefore, the result was subjected to fewer confounding and biases of study design.

Second, except for geographic area, end point, and assessment of PD, we added subgroup analysis according to adjustment for covariates, source of control, methodological quality, and assessment of CHD. We found that the populations of America (OR 4.75, 95%CI: 1.50-15.02) had higher risk than Europeans (OR 3.81, 95%CI: 2.46-5.91), and Europeans had higher risk than Asians (OR 3.46, 95%CI: 1.73-6.94). This was different from previous meta-analysis, whose result showed American populations seem to present weaker association between PD and CHD than European ones. If it is due to the individual and social economic factors, why the oral health awareness and healthcare level of European and American populations are higher than Asians, but the trend of

Table 3 Results of overall and subgroups analyses of pooled odds ratios and 95%CIs

Total and subgroup	No. of trials	Heterogeneity		Model	Meta-analysis		
		I^2 (%)	*P*		OR	95%CI	*P*
Total	38	98.59	< 0.001	Random	3.79	2.23-6.43	< 0.001
Adjustment for covariates							
Yes	21	66.02	< 0.001	Random	2.72	2.13-3.46	< 0.001
No	17	98.68	< 0.001	Random	4.62	2.10-10.18	< 0.001
Source of control							
HB	22	98.5	< 0.001	Random	4.04	2.00-8.12	< 0.001
PB	16	80.38	< 0.001	Random	3.08	2.23-4.26	< 0.001
Methodological quality (NOS)							
< 6	11	83.28	< 0.001	Random	3.38	1.75-6.52	< 0.001
⩾ 6	27	98.73	< 0.001	Random	4.16	2.71-6.40	< 0.001
End point							
CHD	31	98.75	< 0.001	Random	3.63	2.00-6.59	< 0.001
MI	7	70.15	< 0.001	Random	4.12	2.35-7.22	< 0.001
Assessment of PD							
ABL	8	97.93	< 0.001	Random	5.57	1.90-16.33	< 0.001
CAL	10	0	0.5	Fixed	2.54	2.13-3.04	< 0.001
CPI	5	90.24	< 0.001	Random	2.76	1.45-5.23	< 0.001
PI	5	91.95	< 0.001	Random	3.12	1.38-7.05	< 0.001
PPD	8	0	0.76	Fixed	3.55	2.39-5.27	< 0.001
Questionnaire	2	0	0.86	Fixed	2.19	1.73-2.77	< 0.001
Assessment of CHD							
CAG	22	73.04	< 0.001	Random	2.85	2.23-3.64	< 0.001
Cardiologists	10	99	< 0.001	Random	5.09	1.71-15.14	< 0.001
ECG	6	60.72	0.03	Random	3.55	2.06-6.12	< 0.001
Ethnicity							
America	4	88.24	< 0.001	Random	4.75	1.50-15.02	0.01
Asia	23	99.01	< 0.001	Random	3.46	1.73-6.94	< 0.001
Europe	11	56.82	0.01	Random	3.81	2.46-5.91	< 0.001

PD: Periodontal disease; CHD: Coronary heart disease; NOS: Newcastle-Ottawa Scale; OR: Odds ratio; CAG: Coronary arteriography; ECG: Electrocardiograph; MI: Myocardial infarction; CAL: Clinical attachment loss; PPD: Periodontal pocket depth; ABL: Alveolar bone loss; CPI: Community periodontal index; PI: Periodontal index.

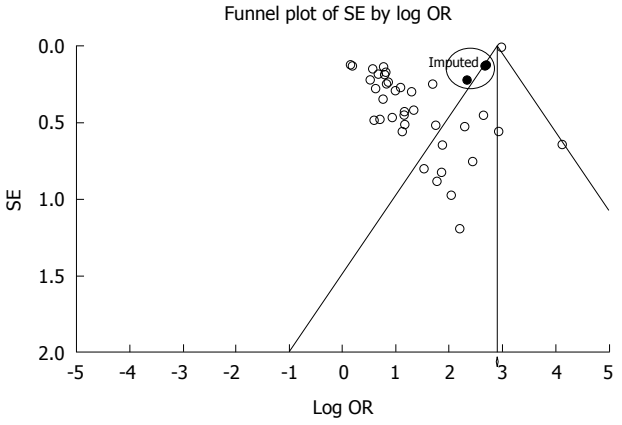

Figure 4 Filled funnel plot with pseudo-95%CIs of the 38 studies. Log of odds ratio (OR) represents the natural logarithm of the OR of individual studies; Standard error by Log OR represents the standard error in the natural logarithm of the OR of individual studies. A circle in the figure represents a study, while a black spot represents an unpublished study which may exist to negate the results of the meta-analysis.

risk is just opposite. Whether other factors, such as racial predisposition of CHD or dietary difference (*e.g.*, Asians like drinking green tea) caused this result still needs to be identified by further researches.

Third, when stratified by adjustment for covariates, the risk of adjusted data was lower (OR 2.72, 95%CI: 2.13-3.46, $P < 0.001$) than unadjusted ones (OR 4.62, 95%CI: 2.10-10.18, $P < 0.001$), and the relevant 95%CI was also narrower. This showed that adjusted data could obtain more precise point estimate than unadjusted data, and also confirmed that PD was an independent risk factor of CHD. When stratified by assessment of CHD, we observed that a definite diagnosis by cardiologists showed higher risk (OR 5.09, 95%CI: 1.71-15.14) than by CAG (OR 2.85, 95%CI: 2.23-3.64) or ECG (OR 2.06, 95%CI: 2.06-6.12). This may be because that objective diagnostic approach is more accurate than subjective one, therefore, similar researches in future combining objective and subjective diagnostic approaches would be more beneficial to confirm CHD. The high methodological quality studies obtained narrower CI (OR 4.16, 95%CI: 2.71-6.40) than low quality ones (OR 3.38, 95%CI: 1.75-6.52), and this was in accordance with PB (OR 3.08, 95%CI: 2.23-4.26) compared with HB (OR 4.04, 95%CI: 2.00-8.12). It could be concluded that high methodological quality and PB study can more effectively control confounding bias.

Some limitations also should be indicated. The major limitation of this meta-analysis was the clinical heterogeneity among the studies with regard to both outcome and exposure definitions. Although we performed subgroup analyses according to the possible sources of heteroge-

neity, clinical heterogeneity also could not be removed completely. However, the result of sensitivity analysis supported that overall result was not influenced by any included single study. Second, 17 studies did not adjust covariates, and the pooled results also showed that the risk reduction sequence was unadjusted, followed by total (combined with adjusted and unadjusted), and adjusted. This means that the overall result may exaggerate the risk. Third, this study only included articles published in Chinese and English, and articles in the other languages (representing the populations of other races) were underrepresented. The funnel plot, Egger linear regression test, and "trim and fill" method also indicated publication bias. Finally, according to the the American Association of Periodontology in 1999, PD should be confirmed by the measure of clinical attachment loss (CAL). However, other periodontal outcomes such as periodontal pocket depth, alveolar bone loss, community periodontal index, periodontal index, or by dentist according to questionnaire were conducted in 28 included studies. This variety of criteria leads to careful interpretation of the meta-analysis results.

In conclusion, this meta-analysis indicated that PD was associated with CHD risk independently and significantly, and we can conclude that an effective oral hygiene regimen would effectively prevent the progression of CHD, an effective PD intervention treatment can control CHD, and correct and effective brushing of teeth, use of dental floss, and regular periodontal scaling would be the simplest and most cost-effective actions. However, whether this is a causal association or PD is only a marker of CHD needs to be confirmed by well-designed studies with larger sample sizes and by taking the certain genetic or environmental confounding factors into account; and whether periodontal interventions are effective also needs to be validated by high quality studies with strict design, large sample size and the standardized implementation, and multi-center randomized controlled trials.

COMMENTS

Background

Growing evidence indicated that periodontal disease (PD) might be associated with coronary heart disease (CHD), however, results from these studies were inconsistent. Thus, whether PD is a risk factor of CHD remains to be clarified.

Research frontiers

CHD is one of the major causes of mortality, account for nearly 30% of deaths worldwide; PD is one of the major two oral diseases and affect up to 90% of the worldwide population. Therefore, it is very important to identify the association between PD and CHD, in order to provide evidence for prevention and treatment of the diseases.

Innovations and breakthroughs

This is a comprehensive meta-analysis, in which the authors performed subgroup analyses to identify the similarities and differences between the adjustment for covariates, source of control, methodological quality, end point, assessment of PD, assessment of CHD, and ethnicity. All these analyses indicated that PD is a risk factor for CHD.

Applications

According to this meta-analysis, an effective oral hygiene regimen would effectively prevent the progression of CHD, an effective PD intervention treatment can control CHD, and correct and effective brushing of teeth, use of dental floss, and regular periodontal scaling would be the simplest and most cost-effective actions. In addition, whether this is a causal association or PD is only a marker of CHD, and whether periodontal interventions are effective remain to be confirmed.

Peer review

The authors have made a good meta-analysis, complete and deep enough.

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