Periodontal Disease and Risk of Chronic Obstructive Pulmonary Disease: A Meta-Analysis of Observational Studies

Xian-Tao Zeng¹, Ming-Li Tu², Dong-Yan Liu¹, Dong Zheng³, Jing Zhang², Wei-Dong Leng¹, ²

¹Department of Stomatology, Taihe Hospital, Hubei University of Medicine, Shiyan, Hubei Province, People’s Republic of China, ²Department of Respiratory Medicine, Taihe Hospital, Hubei University of Medicine, Shiyan, Hubei Province, People’s Republic of China, ³School of Stomatology, Hubei University of Medicine, Shiyan, Hubei Province, People’s Republic of China

Abstract

Background: Many epidemiological studies have found a positive association between periodontal disease (PD) and risk of chronic obstructive pulmonary disease (COPD), but this association is varied and even contradictory among studies. We performed a meta-analysis to ascertain the relationship between PD and COPD.

Methods: PubMed and Embase database were searched up to January 10, 2012, for relevant observational studies on the association between PD and risk of COPD. Data from the studies selected were extracted and analyzed independently by two authors. The meta-analysis was performed using the Comprehensive Meta-Analysis software.

Results: Fourteen observational studies (one nested case-control, eight case-control, and five cross-sectional) involving 3,988 COPD patients were yielded. Based on random-effects meta-analysis, a significant association between PD and COPD was identified (odds ratio = 2.08, 95% confidence interval = 1.48–2.91; P<0.001), with sensitivity analysis showing that the result was robust. Subgroups analyses according to study design, ethnicity, assessment of PD/COPD, and adjusted/unadjusted odds ratios also revealed a significant association. Publication bias was detected.

Conclusions: Based on current evidence, PD is a significant and independent risk factor of COPD. However, whether a causal relationships exists remains unclear. Moreover, we suggest performing randomized controlled trials to explore whether periodontal interventions are beneficial in regulating COPD pathogenesis and progression.

Introduction

Periodontal Disease (PD) is a group of inflammatory diseases that affect the supporting tissues of the teeth. At least approximately 33% dentate adults aged between 30 and 90 years old in the United States experience PD [1], and this disease can affect up to 90% of the global population [2]. Based on the theory of “focal infection” which emerged at the beginning of the twentieth century, many studies have investigated a possible role for PD as a risk factor for systemic conditions over the past two decades [3], including cardiovascular diseases [4], diabetes [5], adverse pregnancy outcome [6], osteoporosis [7], rheumatoid arthritis [8], and Chronic obstructive pulmonary disease (COPD) [9,10].

COPD is the third leading cause of death in the United States, affecting as many as 24 million Americans and resulting in 700,000 hospital admissions, and 124,000 deaths annually [11]. COPD is also an inflammatory disease characterized by the progressive deterioration of pulmonary function and increasing airway obstruction, includes chronic bronchitis and emphysema [12]. In line with the relationship between the anatomical position of oral cavity and pulmonary infection, oral bacteria can be easily carried into the lung and cause infection [13]. In addition, PD and COPD share the same risk factors, including smoking, age, obesity, socioeconomic status, and living conditions [3]. These data strongly suggest that PD may be a risk factor for COPD and that oral bacteria may play a key role in its progression.

This hypothesis has received rapidly growing interest in the past years, and the relationship between PD and COPD has been increasingly recognized over the last two decades. Many epidemiological studies [14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35] have investigated the link between PD and risk of COPD, and most found a positive association. However, different studies have used different measurement methods and investigated different populations, and the magnitudes of the said association are varied and even contradictory among studies. Moreover, the possible role...
of PD in the pathogenesis of COPD remains an important but unresolved issue.

Two previous systematic reviews [9,10] combined several epidemiological studies and reported an association between respiratory diseases and oral health, involving PD and COPD. One review [9] reported a weak association between PD and COPD based on two case-control studies [14,16] and two cross-sectional studies [15,34] of poor to fair quality, whereas the other [10] demonstrated a potential association between PD and COPD based on one case-control study [14] and three cross-sectional studies [15,18,34]. The evidence from each work is limited because only four studies were available and the conventional risk factors were not adjusted in the analysis. The presence of common conventional risk factors, such as smoking, renders the results questionable. Furthermore, whether PD is an independent risk factor for or merely a silent marker of COPD remains unclear.

An improved understanding of this issue may have important public health and clinical implications given the possibility that prevention and treatment of PD might reduce the incidence of COPD. The objectives of this study were to (1) evaluate the inconsistent results from published observational studies on the association between PD and COPD by conducting a meta-analysis and (2) gain a more robust estimate association. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [35] guidelines to report this meta-analysis.

Methods

Literature search

We initially identified published studies that investigated the association between PD and risk of COPD by searching the PubMed and Embase databases from their inception through to January 10, 2012. The following search terms were used: (1) “periodontal disease” or “paradontosis” or “parodontopathy” or “periodontal” or “gum disease” or “periodontium”, and (2) “chronic obstructive pulmonary disease” or “COPD” or “chronic bronchitis” or “emphysema”, without restrictions. We also reviewed the reference lists of retrieved articles and recent reviews.

Study selection

We included any study that met all of the following criteria: (1) the study was of a cross-sectional, case-control, or cohort design; (2) clear diagnostic criteria for PD and COPD were established; (3) the association between PD and risk of COPD was investigated; and (4) the odds ratios (ORs)/risk ratio (RR, for cohort studies) and the corresponding 95% confidence intervals (CIs), or the number of events that can calculate them were reported. Two authors independently evaluated the eligibility of all studies retrieved from the databases. Disagreements were resolved by discussion or in consultation with a third author.

Data extraction

Two reviewers independently extracted data about the characteristics of each study by using a standardized data collection form. Data were recorded as follows: first author’s last name, year of publication, country of origin; characteristics of study population and age at baseline; number of participants with PD and total number of participants, ascertainment of PD; assessment of COPD; and statistical adjustments for confounding factors. Any disagreements were resolved by consensus.

Statistical analysis

We proposed that results from single studies be pooled by meta-analysis where this was found to be both clinically and statistically appropriate. We computed pooled ORs/RRs and relevant 95% CIs using Comprehensive Meta-Analysis software, Version 2.2 (Biostat, Englewood, NJ, USA) [36] to generate forest plots, determine whether a statistical association between PD and risk of COPD exists, and assess the heterogeneity of the selected studies. Heterogeneity was quantified using the $I^2$ statistic [37], with the
Table 1. Study characteristics of included studies.

| Reference          | Design | Location | Group   | Subject | Age(yrs) | Gender(♂/?♀) | Assessment of PD | Assessment of COPD | Adjustment for Covariates | OR(95%CI)          |
|--------------------|--------|----------|---------|---------|----------|--------------|------------------|--------------------|------------------------|---------------------|
| Hayes et al 1998   | NCC    | USA      | COPD    | 261     | 45.0±9.7 | 261/0        | ABL              | FEV1               | age, smoking, education, and height | 1.77(1.27,2.48)     |
| Control            |        |          |         | 857     | 42.18±9.1| 857/0        |                  |                    |                        |                     |
| Scannapieco et al 1998 | CS    | USA      | COPD    | 77      | NA       | 45/32        | OHI              | Self-reported      | NA                    | 4.5(1.06,18.99)     |
| Control            |        |          |         | 309     |          | 137/172      |                  |                    |                        |                     |
| Russell et al 1999 | CC     | USA      | COPD    | 28      | 75.9±8.1 | 14/14        | PI               | Self-reported      | NA                    | 15.1(1.59,130.23)   |
| Control            |        |          |         | 30      | 75.1±5.9  | 12/18        |                  |                    |                        |                     |
| Scannapieco et al 2001 | CS    | USA      | COPD    | 810     | 51.2±17.9| 304/506      | CAL              | FEV1/FVC           | age, gender, race and ethnicity, and education, income, number of dental visits, pack years of smoking, alcohol consumption, and diabetes mellitus | 1.45(1.02,2.05)     |
| Control            |        |          |         | 12,982  | 43.9±17.7 | 6,161/6,821  |                  |                    |                        |                     |
| Garcia et al 2001  | CS     | USA      | COPD    | 279     | NA       | NA           | ABL              | FEV1               | age, height, smoking, alcohol, and education | 1.75(1.33,2.30)     |
| Control            |        |          |         | 833     |          |              |                  |                    |                        |                     |
| Hyman et al 2004   | CS     | USA      | COPD    | 993     | 62.32±14.07| 3,636/2,296  | CAL              | GOLD criteria      | age, gender, race/ethnicity, history of hypertension, history of heart attack, dental visit within 1 year, body mass index, smoking, and family income | 1.48(0.90,2.43)     |
| Control            |        |          |         | 6,632   | 47.37±14.23| 371/662      |                  |                    |                        |                     |
| Kowalski et al 2005| CC     | Poland   | COPD    | 100     | 63.1±10.17| 68/32        | PI               | FEV1/FVC           | NA                    | 3.59(1.84,6.98)     |
| Control            |        |          |         | 101     | 65.3±10.36| 38/63        |                  |                    |                        |                     |
| Leuckfeld 2008     | CS     | Norway   | COPD    | 130     | 54.9±4.9  | 50/80        | ABL              | GOLD criteria      | age, gender, and smoking | 10.0(1.03,97.47)   |
| Control            |        |          |         | 50      | 47.0±9.8  | 29/21        |                  |                    |                        |                     |
| Fatemi et al 2009  | CC     | Iran     | COPD    | 30      | 53±7      | NA           | CAL              | PFT                | NA                    | 1.80(1.46,2.22)     |
| Control            |        |          |         | 30      | 54±5      |              |                  |                    |                        |                     |
| Wang 2009          | CC     | China    | COPD    | 306     | 63.94±9.84| 210/96       | CAL              | GOLD criteria      | age, gender, smoking, and body mass index | 1.00(0.99,1.01)     |
| Control            |        |          |         | 328     | 63.26±8.98| 164/164      |                  |                    |                        |                     |
| Deo et al 2009     | CC     | India    | COPD    | 150     | 41.43±7.53| 140/10       | CAL              | FEV1/FVC           | NA                    | 1.11(0.79,1.56)     |
| Control            |        |          |         | 50      | 43.625±53 | 38/12        |                  |                    |                        |                     |
| Prasanna 2011      | CC     | India    | COPD    | 50      | 56.3±3.8  | 50/0         | PI               | PFT                | NA                    | 3.12(2.53,3.85)     |
| Control            |        |          |         | 50      | 47.4±4.9  | 27/23        |                  |                    |                        |                     |
| Si et al 2012      | CC     | China    | COPD    | 581     | 63.9±9.4  | 422/159      | PI               | FEV1/FVC           | age, gender, occupation, educational level and smoking status | 9.01(3.98,20.40)    |
low, moderate, and high to $I^2$ values of 25%, 50%, and 75%
respectively [30]. Where the $I^2$ value was 25% or lower, indicating
no evidence of heterogeneity, we used the fixed-effect model;
otherwise, we used the random-effects model.

In the presence of heterogeneity, 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 a single study on the overall risk estimate by
sequentially removing study to test the robustness of the main
results.

Where possible, potential publication bias was assessed by visual
inspection of the funnel plots of the primary outcome. The Egger
linear regression test was used to examine the association between
mean effect estimate and its variance [39]. In addition, to assess
the effect of possible publication bias, we calculated the number of
unpublished studies that would have to exist to negate the results
and the pooled OR adjusted for publication bias using the trim
and fill method [40].

Results

Study identification

Of 179 records found initially, 14 articles involving 1 nested
case-control study [14], 8 case-control studies
[16,20,22,23,24,25,26,27], and 5 cross-sectional studies
[15,18,19,21,27,34] were included in this meta-analysis. A detailed
flowchart of the selection process is shown in Figure 1.

Study characteristics

Table 1 presents the major characteristics of the 14 studies for
which information was available. These studies focused on COPD
only. Sample sizes ranged from 58 to 13,792, representing 3,988
COPD patients and 22,871 controls subjects. One study provided
results for males only [14], whereas another did for males in the
COPD group and both sexes in the control group [25]; data for 2
studies [18,23], and 10 others reported results for both sexes
[15,16,19,20,21,22,24,26,27,34]. Of the principal studies, 6, 2,
and 3 were conducted in the United States [14,15,16,19,21,27,34],
India [22,25], and China [24,26,27], respectively; 1 study each
was conducted in Poland [20], Norway [21], and Iran [23].

PD and risk of COPD

Figure 2 shows the results from the random-effects model
pooling the ORs and 95% CIs for COPD. Of all 14 studies, four
studies show there are no statistical differences [19,22,24,27]; six
studies show that population with PD face more than double risk
of developing COPD compare with without ones [15,16,20,21,22,24,26,27,34]. Of the principal studies, 6, 2,
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Subgroup and sensitivity analyses

Table 2 shows the results of subgroup analyses by study design,
etnicity, assessment of PD, assessment of COPD, and adjustment
for covariates. All these analyses indicated that PD is a risk factor
for developing COPD, except for the clinical attachment loss
(CAL) (OR = 1.32, 95% CI = 0.97–1.80; $P = 0.07$) and GOLD
criteria (OR = 1.31, 95% CI = 0.76–2.24; $P = 0.33$). When strat-
ified by adjustment for covariates, all the eight studies have
adjusted smoking [14,18,19,21,24,26,27,34], and the risk of
adjusted studies is lower (OR = 1.78, 95% CI = 1.23–2.58;
Figure 2. Forest plot of PD and risk of COPD, studies are pooled with random-effects model. The pooled OR was represented by a diamond of standard height, with the width indicating the 95% CI. PD, periodontal disease; COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; NCC, nest case-control study; CC, case-control study; CS, cross-sectional study. doi:10.1371/journal.pone.0046508.g002

![Forest plot of PD and risk of COPD](image1)

Figure 3. Forest plot of sensitivity analysis by removing each study in each turn. The pooled OR was represented by a diamond of standard height, with the width indicating the 95% CI. PD, periodontal disease; COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; NCC, nest case-control study; CC, case-control study; CS, cross-sectional study. doi:10.1371/journal.pone.0046508.g003

![Forest plot of sensitivity analysis](image2)
than unadjusted ones (OR = 2.40, 95% CI = 1.52–3.81; P = 0.001), and the relevant 95%CI is also narrower. Sensitivity analysis was performed by sequentially removing each study. The significance of pooled ORs was not greatly influenced by the omission of any single study (the values of ORs are between 1.87 and 2.23, and the relevant 95%CIs are between 1.34 and 3.22), suggesting that the results of this meta-analysis are stable (Fig. 3).

Publication bias

Figure 4 shows that the funnel plot was asymmetrical, indicating the presence of publication bias. The Egger linear regression test also detected moderate publication bias among studies (OR = 3.43, 95%CI = 1.76–2.00; 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 two possible missing studies (black spots in Fig. 4). The estimated OR including the “missing” studies did not substantially differ from our estimate with adjustment for missing studies (OR = 1.94, 95%CI = 1.40–2.70).

Discussion

COPD includes chronic bronchitis and emphysema, Murray et al has predicted that COPD would become the third most common cause of death and the fourth most important disease leading to disability by 2020 [41,42]. PD is considered a novel risk factor, in addition to smoking, chronic exposure to hazardous air pollutants, and genetic conditions [43]. Our meta-analysis of one nested case-control study, eight case-control studies, and five cross-sectional studies provides evidence that PD is associated with an increased risk of COPD and can increase a significantly the risk by 2.08 times. When the subjects were stratified by ethnicity, this association did not differ: the ORs were 1.69 for North Americans (95%CI = 1.43–2.00), 1.93 for Asians (95%CI = 1.15–3.26), and 3.89 for Europeans (95%CI = 2.05–7.38). When the analysis was restricted to studies with control for conventional risk factors, including age, gender, and especially smoking, PD was identified as a probable independent risk factor for COPD (OR = 1.78, 95%CI = 1.23–2.58; P<0.001). When the groups were stratified the group by study design, the results also suggested that PD is a significant risk factor for COPD in both case-control and cross-sectional studies, with the association gaining more powerful from the cross-sectional studies (OR = 1.35, 95%CI = 1.38–3.70; P<0.001) to the case-control studies (OR = 2.26, 95%CI = 1.38–3.70; P<0.001) to the nested case-control study (OR = 2.77, 95%CI = 1.27–2.47; P<0.001). This finding can be attributed to the fact that the cross-sectional study design suffers from more confounding biases compared with the case–control study design and the case–control study design suffers from more confounding biases compared with the nested case–control study design. The prospective cohort study design is the best among observational studies, and it can control confounding biases very well. We therefore suggest that this study design be used in future research.

P<0.001) than unadjusted ones (OR = 2.40, 95% CI = 1.52–3.81; P<0.001), and the relevant 95%CI is also narrower. Sensitivity analysis was performed by sequentially removing each study. The significance of pooled ORs was not greatly influenced by the omission of any single study (the values of ORs are between 1.87 and 2.23, and the relevant 95%CIs are between 1.34 and 3.22), suggesting that the results of this meta-analysis are stable (Fig. 3).

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Oral cavity has been recognized as a potential reservoir for respiratory pathogens [32], and dental plaque may play an important role in its formation, which may also contribute to PD [44]. Colonization of dental plaque by respiratory pathogens followed by aspiration has been proposed as a possible mechanism, but data on whether the same pathogens are isolated in PD and COPD exacerbations are limited. Epidemiological studies have found evidence favoring this association; however, debate on this issue has ensued over recent decades. Our meta-analysis detected a significant association between PD and COPD with and without adjustments made on the conventional risk factors. This suggests that an effective oral hygiene regimen would effectively prevent the progression of COPD, and that an effective PD intervention treatment should be able to control COPD. Correct and effective brushing of teeth, use of dental floss, and regular periodontal scaling would be the simplest and most cost-effective actions. To substantiate these findings, we recommend that sufficient relevant randomized controlled trials be carried out to test whether periodontal interventions can affect the progression of COPD. Moreover, we suggest that fundamental studies investigating the true mechanism between PD and COPD be performed, particularly to identify which role or roles would take much of the responsibility and whether the pathogens isolated in PD exacerbations are the same as those isolated in COPD exacerbations — which can give clearer guidelines for clinical practice and make the link between the two diseases more convincing. In addition, a spacer device and cold water for rinsing should be used in COPD patients undergoing treatment that requires steroid inhalation to reduce the accumulation of steroids in the mouth cavity; similarly, when a metered-dose inhaler is used for steroid inhalation, a spacer device should be applied to reduce the possibility for respiratory pathogens in dental plaque to move into the lung.

The main strength of this study was pooling data from individual studies with small sample sizes and a low statistical power via meta-analysis approach. We also collected studies as relevant as possible and used subgroup and sensitivity analyses to test the robustness of the results. This meta-analysis overcome the shortcomings of two pervious systematic reviews (our meta-analysis also included the five studies [14,15,16,18,34] that used in those systematic reviews) [9,10]. However, this study also had some limitations. First, although meta-analysis is a useful tool in epidemiology, problems associated with methodology may limit its benefits. Case-control study and cross-sectional studies are not the best designs among observational studies; thus, evidence from these studies is likely to be less accurate and possibly more influenced by recall bias compared with that from cohort studies. In addition, meta-analysis is a secondary analysis approach and has some inevitable biases. Second, some pooled ORs were obtained from heterogeneous studies, although we performed sensitivity analyses. Third, the funnel plot of publication bias showed that it was asymmetrical, and publication bias thus had to be considered. This suggests that we may have missed important unpublished studies with results inconsistent with our findings, although we did our best to collect all relevant studies. The filled funnel plot showed that two additional unpublished studies are needed to negate the results of our meta-analysis. Fourth, none of the 14 studies were selected in our meta-analysis provided the degrees of PD and risk of COPD such that we could not conduct a dose-response analysis to assess their relationship more precisely. Fifth, the prevalence/incidence of COPD in developing countries (where access to dental care is limited) is presumably much higher than that in developed countries (where access to dental care is better), but we could not obtain current and relevant data to verify this. As PD and COPD
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