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Original Article

Periodontal health and chronic obstructive pulmonary disease stratified by smoking: a meta-analysis

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Abstract: Periodontitis has been implicated to be a risk factor for chronic obstructive pulmonary disease and cigarette smoking is thought to be the principal risk factor for COPD. We performed this meta-analysis to explore the possible interaction between periodontal health and cigarette smoking in the development of COPD. We retrieved the relevant articles from PubMed, EMBASE and CNKI databases. Studies were selected using specific inclusion and exclusion criteria. Pooled odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. All analyses were performed using the Stata software. Five studies were included in this meta-analysis. Among current smokers, there was an overall increased risk for COPD when the periodontal health was assessed by plaque index (PI) (OR=3.99, 95% CI=2.58 to 6.16). However, no association was found between PI and COPD for either nonsmokers or former smokers. In conclusions, clinical attachment level (CAL), bleeding index (BI) or probing depth (PD) did not increase COPD risk for nonsmokers, current smokers and former smokers. There may be an interaction between periodontal health-related factor plaque index and cigarette smoking in the development of COPD.

Keywords: Periodontal health, smoking, meta-analysis, risk factors

Introduction

Periodontitis is a chronic infectious disease of tooth-supporting tissues (gums, periodontal ligament, alveolar bone and cementum), and often results in the inflammatory destruction of the supporting tissues. Recent studies have implicated that periodontitis is a risk factor for systemic chronic diseases, including cardiovascular diseases, diabetes, rheumatoid arthritis and Chronic obstructive pulmonary disease (COPD) [1, 2].

COPD, one of the most common global health problems, has a high morbidity and mortality over the world [3]. COPD is an abnormal inflammatory response of the lung to noxious particles or gases, accompanied by progressive decline of lung function and aggravation of airway obstruction, and can influence the patient's life quality seriously. Those oral pathogens can be easily carried into the lung and cause lung infections may explain the association between periodontal health and COPD [4]. However, the precise mechanism remains unknown.

Besides, cigarette smoking is thought to be the principal risk factor for both periodontitis and COPD. So we want to know whether there exists an interaction between cigarette smoking and periodontitis, which may affect the progression of COPD. One study reported a significant association between periodontitis and COPD, and the odds ratios (ORs) of plaque index (PI) were 8.28 (95% CI=2.36-29.0), 5.89 (95% CI=2.64-13.1), and 2.46 (95% CI=1.47-4.10) for current, smokers, and non-smokers, respectively [5]. Another case-control study found that periodontal health was significantly associated with an increased risk of COPD among nonsmokers and former smokers [6]. On the contrary, in Jeffrey' research, there was no statistically significant association between periodontitis and COPD among non-smokers or former smokers [7].

Different studies reached different and even totally contradictory conclusions, and these conflicting conclusions may result from population differences, small sample sizes and the difference of measurement methods. Therefore, we performed this meta-analysis of five published case-control studies to explore the possible interaction between periodontal health and cigarette smoking in the development of COPD, and to our knowledge, this was the first

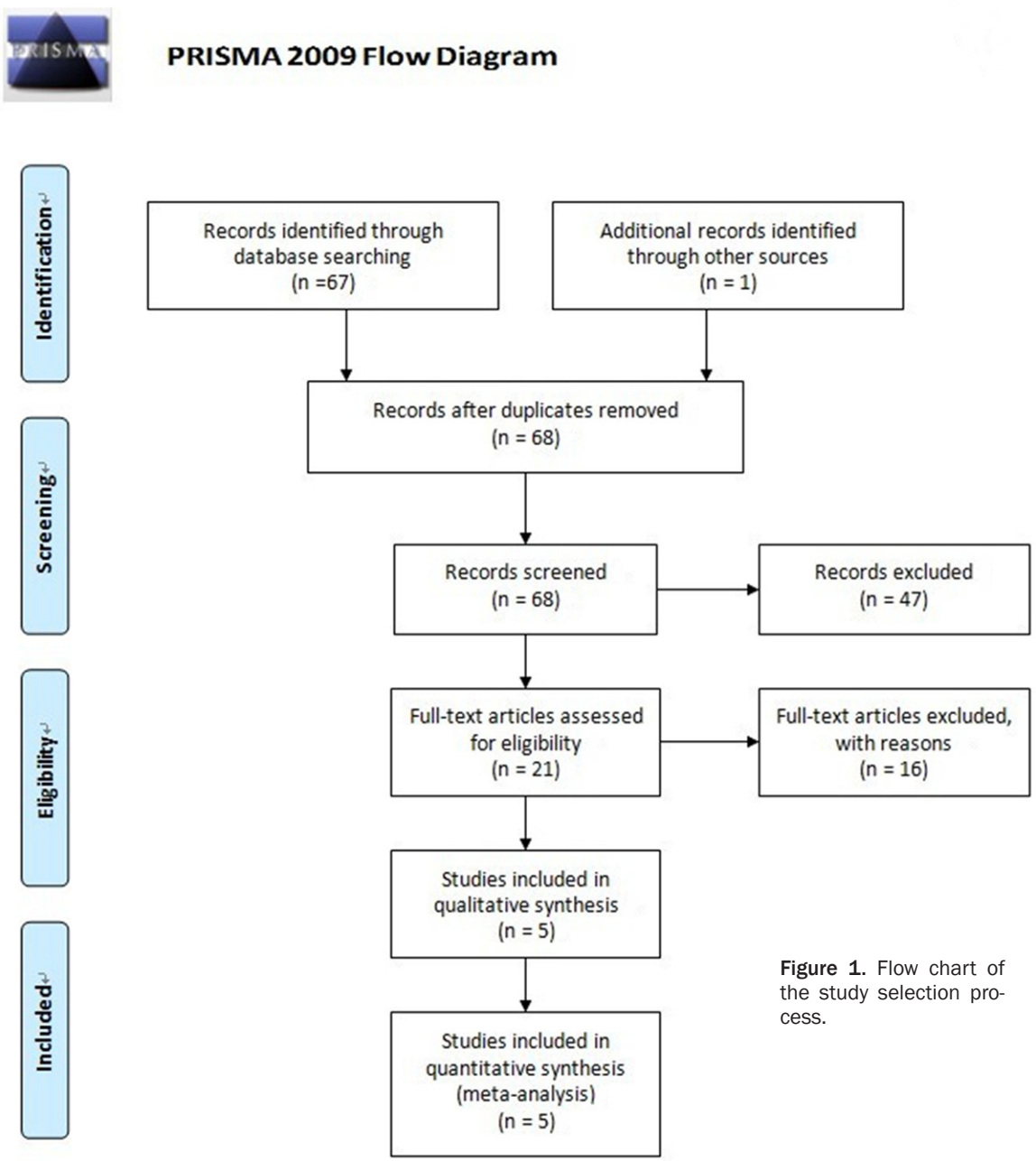

Figure 1. Flow chart of the study selection process.

meta-analysis stratified by cigarette smoking to estimate the association of periodontal health and COPD.

Materials and methods

Data sources

We retrieved the articles using the following terms "periodontal health or periodontitis or periodontal disease" and "Chronic obstructive pulmonary disease or COPD or chronic bronchitis or emphysema" from PubMed, EMBASE and Chinese National Knowledge Infrastructure (CNKI) without restrictions before Aug 2015. We evaluated potentially relevant publications by examining their titles and abstracts, and also screened the reference lists of the obtained articles.

Study selection and data extraction

Eligible studies were selected according to the following inclusion criteria: (1) Both periodontitis and COPD meet the clinical golden diagnostic criteria. (2) Using the methodology of a case-

Table 1. Characteristics of all studies in meta-analysis

Author, year	Country	Ethnicity	Smoke status	Indicator	No. (case /control)	OR	OR 95% CI Lower	Upper	Adjusted factors
Hyman and Reid 2004	American	Cacausian	Nonsmoker	CAL		0.6	0.3	1.2	Age, gender, rac/ethnicity, history of hypertension, history of heart attack, dental visit within 1 year, BMI, year s and family income
			Former	CAL		0.63	0.27	1.48	
			Current	CAL		3.71	1.74	7.89	
			Total	CAL	112/220	1.48	0.9	2.43	
Deo et al. 2009	India	Asian	Total	CAL	150/50	1.6	0.72	3.55	No adjusted
			Nonsmoker	CAL		4.66	0.24	88.96	
			Current	CAL		1.52	0.67	3.64	
			Total	BI		3	1.01	8.88	
			Nonsmoker	BI		1.39	0.28	7.05	
			Current	BI		2.85	0.67	12.18	
			Total	PI		3.69	1.91	7.13	
			Nonsmoker	PI		0.31	0.01	7.02	
			Current	PI		5.07	2.64	9.74	
Si et al. 2012	China	Asian	Total	PD	640/379	0.19	0.07	0.5	Age, sex, occupation, educational level
			Total	PI		9.01	3.98	20.4	
			Total	CAL		1.41	1.09	1.84	
			Current	PI		8.28	2.36	29	
			Current	PD		0.16	0.03	0.84	
			Former	BI		0.23	0.13	0.41	
			Former	PI		5.89	2.64	13.12	
			Former	AL		1.59	1.24	2.02	
			Nonsmoker	PI		2.46	1.47	4.1	
			Nonsmoker	ABL		3.89	2	7.57	
			Nonsmoker	PD		0.19	0.06	0.64	
Wang et al. 2009	China	Asian	Nonsmoker	PI	306/328	1.17	0.87	1.59	Age, gender, and body mass index
			Nonsmoker	CAL		1	0.99	1.01	
			Former	PI		1.33	0.73	2.45	
			Former	CAL		0.99	0.99	1.01	

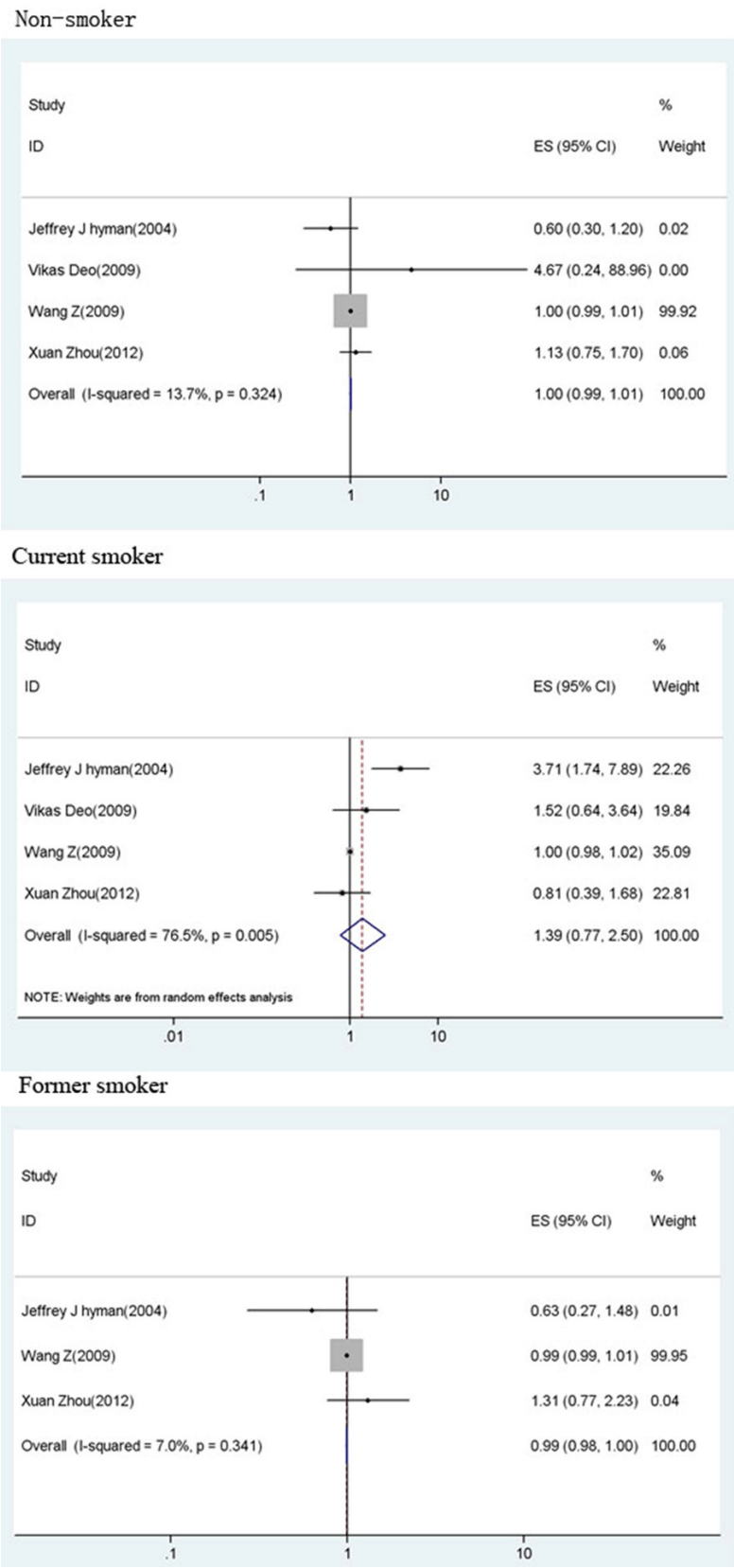

Figure 2. Forest plot for the association of COPD and clinical attachment level by stratified meta-analysis.

control study. (3) Related data of smoking status was reported. (4) There was sufficient published data for the computation of odds ratios (ORs) with 95% confidence intervals (95% CIs).

Duplicate and obviously unrelated articles were eliminated and abstracts of the remaining articles were also examined to determine whether the full-text article should be obtained. A four-phase flow diagram according to Systematic Reviews (http://www.prisma-statement.org/) was shown in **Figure 1**. Data were recorded as follows: first author's name, publication date, country origin, ethnicity, smoking status, involved indicator of periodontal health, total number of cases and controls, corresponding case-control number of each smoking status and indicator, and statistical adjustments for confounding factors.

Statistical methods

Pooled ORs and corresponding 95% CIs were obtained from combination of single studies. After stratifying data of each study according to smoking status (nonsmoker, former smoker and current smoker), we calculated OR of each periodontal health indicator (CAL, PI, PD, BI, ABL) and generated forest plots using the Stata software version 11.0 (Stata Corp, College station, TX).

We examined the heterogeneity of our study by the Cochran's Q test and quantified by I^2 (a significance level of $P < 0.10$ and/or $I^2 \geq 50\%$). We performed initial analy-

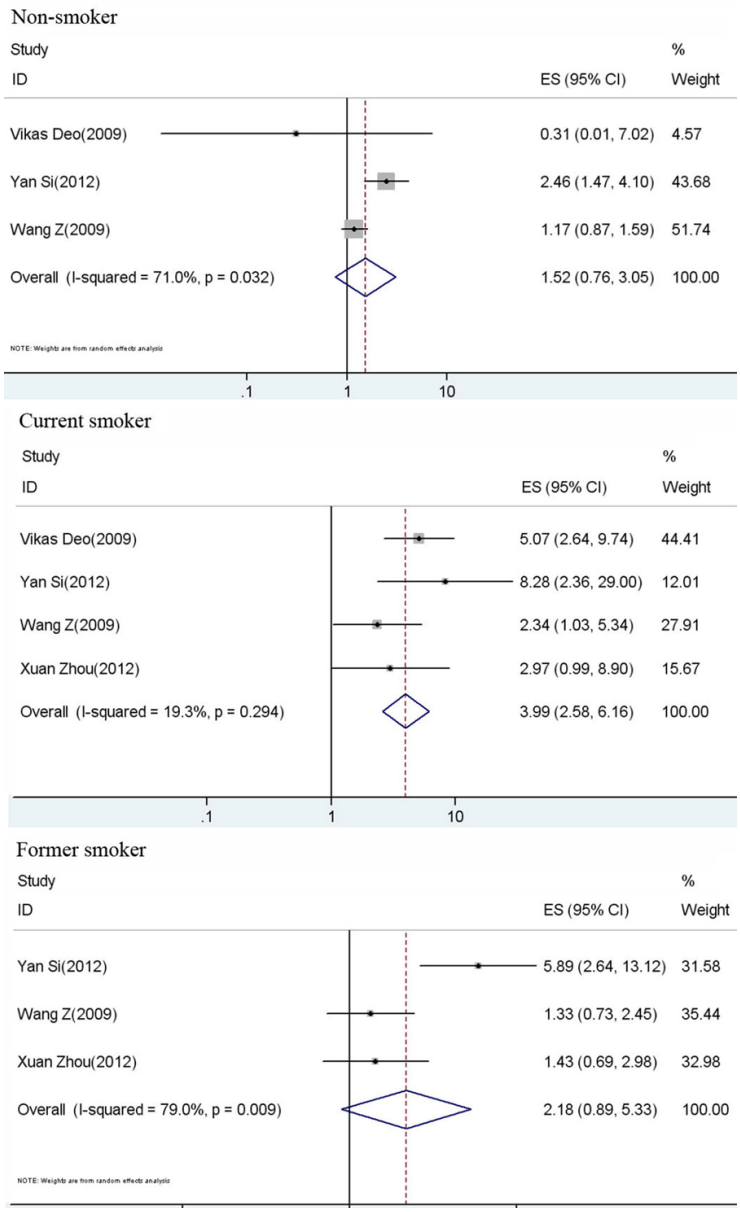

Figure 3. Forest plot for the association of COPD and plaque index by stratified meta-analysis.

ses with a fixed-effect model if there was no evidence of heterogeneity. Otherwise, we used the confirmatory analyses with a random-effect model to get summary statistics for ORs of periodontal health and COPD risk.

We assessed potential publication bias by examining funnel plots and using the Egger's test and the Begg's test. The significance of the intercept was determined by the t test as suggested by Egger's test. Statistical analyses were performed using Stata 10.0.

Results

Table 1 presents the major characteristics of all studies in our meta-analysis. For the five studies, sample sizes ranged from 200 to 1009, representing 1401 COPD patients and 1158 cotrols. There were 4 studies of Asians and 1 study of Caucasians.

The association of COPD and clinical attachment level (CAL) by stratified meta-analysis was showed in forest plot in **Figure 2**. Among nonsmokers, current smokers and former smokers, no association was found between periodontal health-related factor CAL and COPD (OR=1.00, 95% CI=0.99-1.01; OR=1.39, 95% CI=0.77-2.50; OR=0.99, 95% CI=0.98-1.00). Other than curent smokers (I^2=76.5%, P=0.005), there was no evidence of heterogeneity for nonsmokers and former smokers.

Figure 3 showed the forest plot for the association of COPD and PI (plaque index) by stratified meta-analysis. Among current smokers, there was an overall increased risk for COPD when the periodontal health was assessed by PI (OR=3.99, 95% CI=2.58-6.16), and there was no evidence of heterogeneity across studies. However, no association was found between PI and COPD for both nonsmokers and former smokers, and the weights were from random effects analysis (I^2=71.0%, P=0.032; I^2=79.0%, P=0.009).

As seen in **Figure 4**, We did not find any overall association between bleeding index (BI) and COPD risks regardless of smoking status (nonsmoker: OR=1.19, 95% CI=0.58-2.46; current smoker: OR=1.35, 95% CI=0.57-3.24; former smoker: OR=0.37, 95% CI=0.13-1.01). Fixed effect analysis was used for nonsmokers and current smokers, while for former smokers, random effects analysis was performed for heterogeneity (I^2=73.9%, P=0.050).

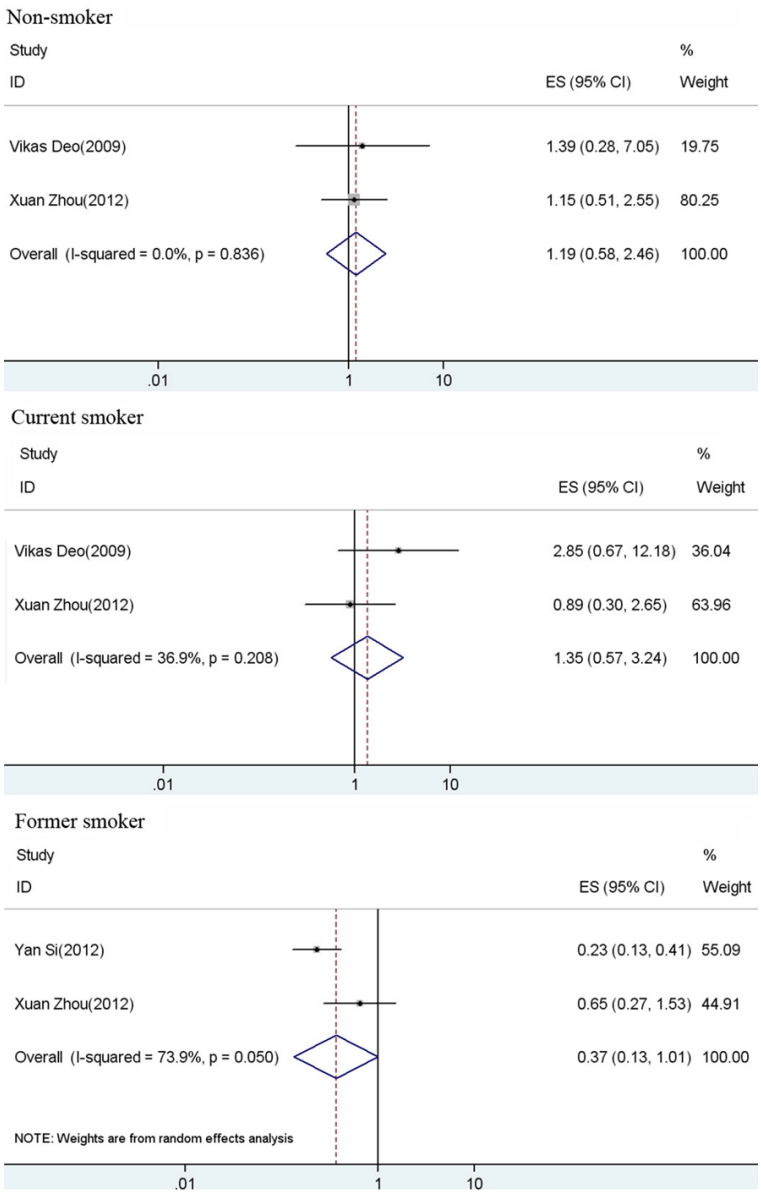

Figure 4. Forest plot for the association of COPD and bleeding index by stratified meta-analysis.

Figure 5 showed the results from the forest plot for the association of COPD and probing depth (PD) by stratified meta-analysis. Results of this meta-analysis indicated that periodontal health-related factor PD did not increase risk to COPD, with OR=0.30 (95% CI=0.15-0.62) and OR=0.43 (95% CI=0.14-1.31) for nonsmokers and current smokers respectively.

Discussion

The present study is the first comprehensive meta-analysis of the association between periodontitis and COPD stratified by cigarette smoking. From this metanalysis of five published case-control studies, we found th-ere may be an interaction between periodontal health and cigarette smoking in the development of COPD. Amo-ng current smokers, there was an overall increased risk for COPD when the periodontal health was assessed by PI (OR=3.99, 95% CI=2.58-6.16), while no significant association was found amo-ng both nonsmokers and former smokers. Both smoking and periodontal health may have an important role in the etiology of COPD. This suggested that we should pay more attention to periodontal health and smoking cessation to reduce the risk of COPD.

Previous studies have suggested the associations be-tween poor oral hygiene and periodontitis with chronic respiratory diseases such as COPD. The study of Hayes et al. found that the level of ABL was independently associated with COPD [8]. Scanapieco and Ho. performed a retrospective study showed that individuals with COPD had hi-gher AL than those without COPD [9]. In a prospective study followed up to 30 years, participants in the increasing quintile of worse periodontal health at baseline had greater risk for developing COPD [10]. An Indian study also showed that the higher mean AL, the higher likelihood of COPD [11]. The study in a Chinese population have reported that patients having less healthy oral behavior and poor oral health knowledge were more likely to have COPD [6]. It is possible that periodontal conditions may combine with other factors, such as smoking, to contribute to the progression of COPD [11]. Cig-arette smoking is the most important and well-known risk factor for COPD and is also a major risk factor for periodontitis. Therefore,

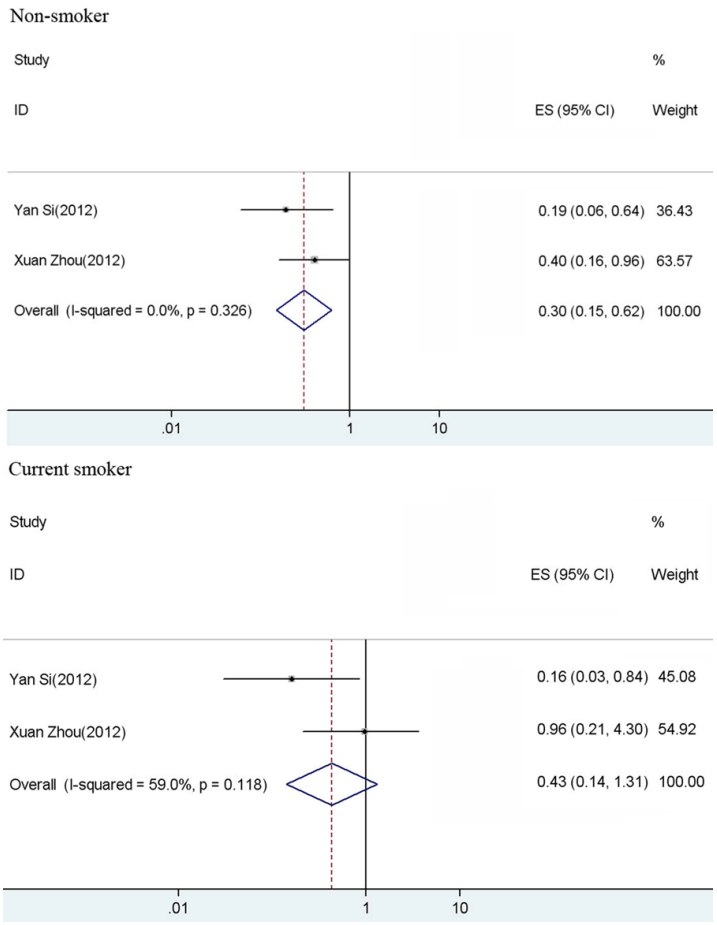

Figure 5. Forest plot for the association of COPD and probing depth by stratified meta-analysis.

smoking could be either a confounder or an effect modifier in the relationship be-tween periodontitis and COPD.

Testing for environment-environment interaction requires large numbers of cases and controls, and meta-analysis may be one way to untangle the disparity among several smaller studies. More than 1000 case-control pairs would be needed to detect an OR interaction of 2.0 with 80% power [12]. Combining five studies in this meta-analysis yielded more than this predicted number, with 1401 cases and 1158 controls. Smaller studies do provide important clues as to whether a potential association exists, but consistency across populations remains a critical confirming step.

The present meta-analysis combined the previous findings in a larger sample and showed consistent and strong relationship between multiple periodontal indices and COPD status. In all the periodontal health indicators, only PI showed a significant association with COPD among current smokers (OR=3.99, 95% CI=2.58-6.16). The biologic mechanisms of how maternal smoking and PI interact in the etiology of COPD remain unk-nown. PI seemed to be the main periodontal health indicator for COPD, which confirmed the conclusion Yan Si's study [5]. Plaque accumulation provide sufficient nutrients and suitable living environment for oral and pulmonary pathogens, and these pathogens can be easily carried into the lung during the process of breathing and swallowing, which may cause lung infections [4, 13,14].

One of the results of this meta-analysis showed that periodontal health indicator PD did not increase risk to COPD, with OR=0.30 (95% CI=0.15-0.62). First, it should be noted that only two studies provided relevant data, so small sample size may have contributed to this result. Second, one study speculated that those with comparable levels of PD were younger than those with other indicators, and this result reflected the residual effects of age [7].

Despite trying our best to perform a comprehensive meta-analysis, the present study has some limitations that should be considered. First, our analysis used published international studies, which could result in inevitable publication bias and distorted the meta-analysis, although the results for publication bias in our study were not statistically significant. Second, testing for pe-riodontal health and cigarette smoking interaction requires large numbers of cases and controls, and the sample size of our study still could not analyze the relationship between periodontal health, cigarette smoking and COPD comprehensively. Third, lack of the original data of available studies limited our further evaluation of potential interactions. Forth, other disease associated cigarette sm-oking may contribute the risk factors to COPD, which need to be investigated.

Conclusion

There may be an interaction between periodontal healthre-lated factor plaque index and cigarette smoking in the development of COPD.

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Disclosure of conflict of interest

None.

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