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Original Article

Incidence of oral candidiasis is associated with inhaled corticosteroids in Chinese patients: a systematic review and meta-analysis

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Abstract: The study aimed to ascertain relationships between inhaled corticosteroid (ICS) and the incidence of oral candidiasis (OC) among Chinese patients. Literature retrieve was performed in databases with predefined strategy. Quality assessment was performed by the Cochrane Collaboration's tool. Risk difference (RD) or risk ratio (RR) with corresponding 95% confidence interval (CI) was used as the effect sizes. OC incidence was detected in different study types. Publication bias was detected by funnel plot and Egger's test. In total, 46 studies were included for the meta-analysis, and the overall quality was moderate. Using ICS did not significantly increase the incidence of OC, compared with non-ICS (RD = 1.40%, 95% CI: -0.30% to 3.10%, P = 0.111) in randomized controlled trials (RCTs). However, higher ICS dose significantly increased the incidence of OC than lower ones (RR = 2.48, 95% CI: 1.23 to 4.99, P = 0.011), and ICS with a spacer device showed a significant decreased incidence than that without the device (RR = 0.37, 95% CI: 0.22 to 0.63, P < 0.001). The overall incidence of OC was 5.1%. Thereinto, the OC incidence was 10.0% in RCTs comparing different ICS dosages, 3.2% in observational studies and 1.4% in RCTs comparing ICS vs. non-ICS. In studies focused on preventing OC, the preventive group achieved a decreased incidence than control group (2.4% vs. 16.4%). Higher ICS dose might be significantly associated with OC incidence in Chinese patients. ICS with a spacer device might reduce the incidence and be more preferable for patients. ICS may not increase the OC incidence given the appropriate prevention.

Keywords: Inhaled corticosteroid, oral candidiasis, dose, spacer device, chinese, meta-analysis

Introduction

Inhaled corticosteroids (ICS) have been widely used for the management of asthma and chronic obstructive pulmonary disease (COPD). ICS could reduce inflammation-driven airflow obstructions via inhibition of inflammation in lower airway tract [1]. However, ICS can result in many local adverse effects such as oral candidiasis (OC), perioral dermatitis, dysphonia, pharyngitis and cough [2]. These side effects could lead to discomfort and reduce the compliance with ICS.

Commonly, OC is the consequence of local immunosuppression caused by the ICS particles deposition in the upper respiratory airways [3]. In immuno-compromised patients, the local infection of OC may enter the bloodstream and eventually progress into a systemic severe infection [4]. Higher dose of ICS for COPD treatment is required to overcome corticosteroid unresponsiveness, and thus is tightly related to high risk of OC [5].

Several studies have evaluated the relationship between ICS and OC incidence. A previous meta-analysis indicated that ICS administration significantly increased the risk of OC at any dose regardless of the device, compared with placebo [6]. Recently, a prescription sequence symmetry analysis retrieving the Inter Action Data Base (IADB) for drug prescription data in 17 years discoveries that ICS is significantly associated with increased risk of OC after the first year of ICS application [3]. Other investigators point out that OC incidence is also related to the ICS dose and device. Results from a study in Turkey show that the frequency of OC is higher in fluticasone propionate 500 microg/d group than controls, while the frequency was not significantly different between the 200

microg/day group and control group [7]. Moreover, the oropharyngeal deposition of ICS can be reduced to about 1/11 by use of a spacer device [8]. However, OC incidence is varied from 0-70% depending on different populations and studies [9], and in Chinese population, no study containing large samples has reported the OC incidence in patients prescribed with ICS. Therefore, we mainly retrieved the Chinese databases and included several eligible articles to perform this meta-analysis. In addition, these studies were classified into three meta-analysis groups based on their different comparisons, such as using *vs*. not using ICS, higher dose *vs*. lower dose, and ICS application with *vs*. without a spacer device. It is expected to provide a comprehensive evaluation about the influence of ICS on OC incidence among Chinese population.

Material and methods

Literature research

The systematical literature retrieve was conducted in databases including Medline, Cochrane, Wanfang database, Chinese National Knowledge Infrastructure (CNKI) and VIP database up to October 30th, 2014. The key searching strings were "oral candidiasis", "inhaled corticosteroid", "adverse effects" and "Chinese". The searching strategies were "Adverse effects" OR "side effects" OR "adverse events" OR "safety" AND "oropharyngeal candidiasis" OR "oral candidiasis" OR "thrush" OR "mouth wash" OR "oral candidal infections" OR "oral candidosis" OR "Candidiasis, Oral" AND "inhaled corticosteroids" OR "inhaled corticosteroid" OR "inhaled steroids" OR "Inhalational steroids" OR "budesonide" OR "Beclomethasone" OR "fluticasone" AND "Chinese" OR "China".

Selection criteria and quality assessment

Clinical studies that involved treatments of chronic airway diseases or airway hyper responsiveness by ICS, and OC occurrence after the ICS application were included for the systemic review. Eligible randomized controlled trials (RCTs) were included to perform the comparative meta-analysis, and single-armed studies that provided available OC incidence data were also pooled by meta-analysis. By contrast, exclusion criteria were: (1) lacked the total number of individuals prescribed with ICS; (2) incidence of OC were unavailable or cannot be calculated; (3) the event of OC could not be separately calculated from other adverse events; and (4) duplicated publications. In addition, we further divided the included studies into three different meta-analysis groups. Studies were included in the meta-analysis evaluating the influence on OC using or not using ICS if they met the criteria of: (a) they were RCTs; (b) the participants were patients who have been not suffered with OC but could be treated with ICS; (c) the treated group was treated with ICS, while the control was without ICS; (d) the endpoint was incidence of OC and detection rate of oropharyngeal candidiasis. Studies were included in the meta-analysis comparing influence of different ICS doses on incidence of OC, if they were: (a) RCTs; (b) the participants were patients who have been not suffered with OC but have treated with ICS; (c) control and treated groups used the same ICS treatment but with different dosages; (d) the endpoint was incidence of OC and detection rate of oropharyngeal candidiasis. Studies were screened out for the meta-analysis comparing effects of ICS using or not using a fog-storage tank on incidence of OC if they were: (a) RCTs; (b) the objects were patients who have been not suffered with OC but have treated with ICS; (c) treated group received ICS using a spacer device, while the control received the same ICS dosage but not using such a device; (d) the endpoint was incidence of OC and detection rate of oropharyngeal candidiasis. Two authors independently completed the retrieve and study selection, and if disagreement appeared, a discussion with a third investigator was required to finally reach a consensus. Additionally, risk of bias of the studies was examined by the Cochrane Collaboration's tool [10].

Statistical analysis

All the included RCTs were classified as four groups: ICS versus (*vs*.) non-ICS; comparison between different ICS dosages (two groups: high dose vs. middle dose; middle dose vs. low dose); and ICS application with *vs.* without a spacer device. Then meta-analyses were carried out to compare the OC incidence. Dosage levels of the ICS was classified according to the Global Initiative for Asthma (GINA) guidelines [11]. Heterogeneity across the selected studies was evaluated based on Cochran Q statistic and I^2-test [12]. If substantial heterogene-

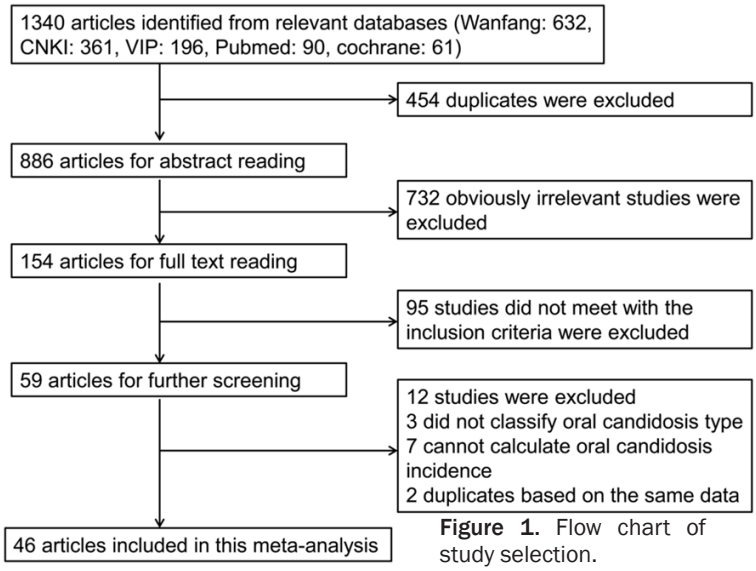

Figure 1. Flow chart of study selection.

ity was observed (P < 0.05, $I^2 \geq 50\%$), a random-effects model was used to calculate the pooled results; whereas a fixed-effects model was applied if obvious homogeneity presented (P > 0.05, $I^2 < 50\%$). In the comparison of ICS *vs.* non-ICS, risk difference (RD) with its corresponding 95% confidence interval (CI) was selected as the effect size to calculate the pooled results because the OC incidence was "0" in some studies. Risk ratio (RR) with 95% CI was used as the effect size in the other comparisons.

Furthermore, the pooled incidence of OC after ICS administration in single-armed studies was also calculated by meta-analysis. Since the incidence was "0" in many observation groups, the continuity correction by 0.5 was performed [13]. A funnel plot and Egger's test were utilized to detect publication bias of the included studies. All the above statistical analyses were implemented using the software of STATA 11.0 (STATA, College Station, TX, USA).

Results

Characteristics of eligible studies

A set of 1340 studies were retrieved from the databases. After removal of duplicated publications, 886 articles were screened out for abstract reading, and 154 studies were selected. Then 59 studies were remained through full text reading. By further screening, 12 studies were excluded (3 did not separate the OC from other adverse events or fungal infections, 7 could not be used to calculate OC incidence and 2 were duplicated publications based on the same population). Finally, a total of 46 eligible articles were included in this meta-analysis. Detailed selection process is presented in **Figure 1**. Among these included articles, there were 12 studies involving 836 cases and 592 controls compared OC incidence between using ICS group and non-using ICS group. Of them, 5 studies [14-17] used dry-powder ICS (DPI), 4 studies [18-21] applied nebulized ICS (NI); whereas 3 studies [22-24] compared effects between ICS and systematic ICS (SCS). Of the above 12 studies, 10 were RCTs. Six studies [17, 25-29] compared influence of different ICS dosages on OC incidence, and 4 of which were RCTs. In addition, 5 studies [30-34] compared influences of ICS application on OC incidence with (222) or without (220) a spacer device. Furthermore, a total of 12 studies [35-47] reported OC incidence during the application of ICS, and 12 studies [48-59] involved the prevention of OC after application of ICS. Basic characteristics of the included RCTs are shown in **Table 1**.

Quality assessment of the eligible studies

As indicated in **Table 2**, most of the included studies did not mention the random selection method or conceal allocation, nor the blind method. However, risk of selection bias and other bias were low. In summary, the overall quality of the included studies was moderate.

Outcomes

Comparison of OC incidence between ICS and non-ICS groups: Unexpected, pooled result of the RCTs indicated that application of ICS did not significantly increase the incidence of OC, compared with non-ICS (RD = 0.8%, 95% CI: -0.9% to 2.4%, P = 0.36), under a fixed-effects model (heterogeneity result: I^2 = 0.0%, P = 0.70) (**Figure 2**). Additionally, whatever the ICS method was applied, the result was not signifi-

Table 1. Characteristics of the included studies

RCTs comparing using vs. non-using ICS										
Author	Year	Study category	Male/all	Age (mean ± SD)	Disease	ICS group	Control group			Follow-up time (d)
Liu et al	2012	RCT	34/60	64±9	Bronchiectasis	Fluticasone 250 ug bid via DPI	Non-ICS			180
Yin et al	2012	RCT	39/47	65±4	COPD stable	Fluticasone 500 ug bid via DPI	Non-ICS			56
Qu et al	2008	RCT	125/152	65±8	COPD stable	Budesonide 400-800 ug/d via DPI	Non-ICS			365
Zheng et al	2007	RCT	397/445	66±8	COPD stable	Fluticasone 500 ug bid via DPI	Non-ICS			168
Yao et al	2013	RCT	78/130	59±2	AECOPD	Budesonide 0.5 mg bid via nebulizer	Non-ICS			7
Weng et al	2011	RCT	37/64	11±2	Asthma exacerbation	Budesonide 1 mg bid via nebulizer	Non-ICS			5
Gu et al	2011	RCT	90/114	78±8	AECOPD	Budesonide 0.5 mg bid via nebulizer	Non-ICS			14
Du et al	2011	RCT	59/102	68±7	AECOPD	Budesonide 1 mg bid via nebulizer	Methylprednisolone 40-80 mg/d			7
Li et al	2009	RCT	46/65	68±15	AECOPD	Budesonide 1 mg bid via nebulizer	Methylprednisolone 40 mg bid			7
Luo et al	2005	RCT	30/72	34±20	Cough variant asthma	Budesonide 200 ug bid via DPI	Prednisone 1 mg/kg'd taper off			28
Meng et al	2008	Self-control study	32/45	68±NA	COPD stable	Budesonide 320 ug bid via DPI	Non-ICS			90
Li et al	2011	Observational study	43/78	68±8	AECOPD	Budesonide 1 mg bid via nebulizer	Non-ICS			7
RCTs comparing ICS of different dose										
Author	Year	Study category	Male/all	Age (mean ± SD)	Disease	ICS	Group 1	Group 2	Group 3	Follow-up time (d)
Gao et al	2013	RCT	38/60	66±10	COPD stable	Fluticasone via DPI	500 ug bid	250 ug bid		180
Liu et al	2012	RCT	60/110	6.5±1.3	Asthma exacerbation	Budesonide via MDI	200 ug bid	200 ug qd		30
Wen et al	2012	RCT	58/76	61±6	COPD stable	Budesonide via nebulizer	400 ug bid	200 ug bid		360
Qu et al	2008	RCT	83/99	65±8	COPD stable	Budesonide via DPI	800 ug/d	400 ug/d		365
Zhu et al	2012	Observational study	91/162	65±NA	COPD stable	Budesonide/Fluticasone	High dose	Medium dose	Low dose	84
Li et al	2014	Observational study	10/18	4.0±0.6	Asthmatic bronchitis	Glucocorticosteroid via nebulizer	High dose	Medium dose	Low dose	120
RCTs comparing using ICS with and without spacer										
Author	Year	Study category	Male/all	Age (mean±SD)	Disease	ICS	Group 1	Group 2		Follow-up time (d)
Lu et al	2014	RCT	38/68	7±NA	Asthma exacerbation	Budesonide 1 mg bid	Nebulizer with spacer	Nebulizer		6
Li et al	2013	RCT	62/114	65±15	COPD stable	Fluticasone 250 ug bid	MDI with spacer	DPI		7
Zhang et al	2013	RCT	99/160	6±3	Asthma stable	Budesonide	MDI with spacer	MDI		365
Guo et al	2012	RCT	35/62	9±2	Asthma stable	Budesonide 200-600 ug/d	MDI with spacer	MDI		365
Zhou et al	2001	RCT	10/38	46±22	Asthma exacerbation	Beclomethasone 800-1200 ug/d	MDI with spacer	MDI		90

RCTs focusing on preventing OC after application of ICS

Author	Year	Study category	Male/all	Age (mean ± SD)	Disease	ICS	Group 1	Group 2	Follow-up time (d)
Ou et al	2014	RCT	182/336	1.2±NA	Asthma/bronchitis/ pneumonia	Budesonide 0.5-1 mg bid-tid via nebulizer	Oral care and rinse	pay no attention to oral care or rinse	5
Huang et al	2014	RCT	172/188	71±8	AECOPD	Glucocorticosteroid via nebulizer	Intensive oral care	Rinse with NS	NA
Fang et al	2013	RCT	NA/100	63±NA	Asthma exacerbation	Budesonide via nebulizer	Rinse under supervision	Rinse freely	14
Li et al	2013	RCT	NA/53	62±NA	Asthma exacerbation/ AECOPD	Budesonide 200 ug bid via MDI	Oral care with 2.5% SB	Oral care with NS	7
Guo et al	2012	RCT	294/428	47±NA	NA	Glucocorticosteroid via nebulizer	Rinse under supervision	Rinse freely	NA
Liang et al	2012	RCT	NA/218	66±NA	Asthma/COPD	Budesonide via nebulizer	Rinse with nystatin	Rinse with water	NA
Shen et al	2011	RCT	NA/198	0.5±NA	Asthmatic pneumonia	Budesonide via nebulizer	Oral care with 2% SB	Without oral care	7
Zhu et al	2011	RCT	NA/150	> 65	AECOPD	Budesonide 2 mg bid via nebulizer	Rinse with nystatin	Rinse with NS	14
Liu et al	2011	RCT	82/114	70±NA	AECOPD	Budesonide 2 mg bid via nebulizer	Rinse with nystatin	Rinse with NS	10
Gao et al	2010	RCT	NA/46	67±NA	Asthma exacerbation/ AECOPD	Budesonide 1 mg bid via nebulizer	Oral care with 2.5% SB	Oral care with NS	7
Xie et al	2009	RCT	132/212	65.6±NA	Asthma exacerbation/ AECOPD	Glucocorticosteroid via nebulizer	Oral care with 2.5% SB	Oral care with water	7
Hu et al	2009	RCT	76/94	65±NA	AECOPD	Budesonide 2 mg bid via nebulizer	Rinse with 4% SB followed by smearing nystatin	Rinse with NS	10

Other studies reported OC incidence during the application of ICS

Author	Year	Male/all	Age (mean ± SD)	Disease	ICS	Follow-up time (d)
Xu et al	2014	6/18	36±NA	Asthma stable	Fluticasone 250 ug bid via DPI	90
Pan et al	2013	51/94	42±2	Asthma exacerbation	Fluticasone 250 ug bid via DPI	28
Xian et al	2013	79/120	43±12	Asthma stable	Fluticasone 250-500 ug bid via MDI	56
Xiang et al	2013	104/200	41±14	Asthma stable	Fluticasone 250 ug bid via DPI	360
Yang et al	2012	NA/1556	NA	AECOPD	Budesonide via nebulizer	NA
Qiu et al	2012	NA/437	NA	COPD stable	Fluticasone via DPI	NA
Sun et al	2011	32/85	46±NA	Asthma stable	Fluticasone 100 ug bid via DPI	84
Zhu et al	2011	NA/62	1.5±NA	Recurrent wheezing	Budesonide 1 mg bid via nebulizer taper off	84
Ma et al	2010	104/188	67±NA	COPD stable	Fluticasone/Budesonide via DPI	90
Zhen et al	2008	60/73	66±20	Asthma exacerbation/ AECOPD	Beclomethasone 2.5 mg q8 h via nebulizer	10
Han et al	2005	97/184	56±13	COPD stable	Budesonide 800 ug/d via MDI	360
Gu et al	2003	34/52	9±NA	Asthma stable	Fluticasone 50-375 ug/d via MDI with spacer	365

RCT: randomized controlled trials; ICS: Inhaled corticosteroids; DPI: dry-powder ICS; COPD: chronic obstructive pulmonary disease; AECOPD: Acute exacerbation ofCOPD; NA: not available; MDI: meter dose inhaler.

Table 2. Risk of bias of the included studies

Author	Year	Random method	Allocation concealment	Blinding method	Complete outcome data	Selective reporting	Other bias
ICS vs. non-ICS							
Liu et al	2012	√	?	×	√	N	N
Yin et al	2012	?	?	×	√	N	N
Qu et al	2008	?	?	×	√	N	N
Meng et al	2008	A before-after study					
Zheng et al	2007	?	?	√	√	N	N
Yao et al	2013	?	?	×	√	N	N
Weng et al	2011	?	?	×	√	N	N
Gu et al	2011	?	?	×	√	N	N
Li et al	2011	A retrospective cohort study					
Du et al	2011	?	?	×	√	N	N
Li et al	2009	?	?	×	√	N	N
Luo et al	2005	×	?	×	√	N	N
High-dose vs. middle-dose (or middle-dose vs. low-dose)							
Gao et al	2013	?	?	?	?	N	N
Lu et al	2012	A cross-sectional study					
Li et al	2014	A retrospective cohort study					
Liu et al	2012	?	?	?	√	N	N
Wen et al	2012	√	?	?	?	N	N
Qu et al	2008	?	?	?	√	N	N
Use vs. non-use NI device							
Lu et al	2014	?	?	×	√	N	N
Li et al	2013	?	?	×	?	N	N
Zhang et al	2013	?	?	×	√	N	N
Guo et al	2012	√	?	×	√	N	N
Zhou et al	2001	?	?	×	√	N	N

Note: ICS: inhaled corticosteroid; NI: nebulized ICS; "√": the item is correctly applied or clearly described; "×": the item is incorrectly used or elaborated; "?": not clearly described; "N": no bias of this item.

cant (DPI: RD = 1.6%, 95% CI: -0.6% to 3.9%, P = 0.15; NI: RD = 0.0%, 95% CI: -2.2% to 2.2%, P = 1.0, **Figure 2**). In the comparison of ICS vs. SCS, there were no significant differences, either (RD = -0.6%, 95% CI: -5.7% to 4.4%, P = 0.80).

Comparison of OC incidence between different ICS dose groups: Higher dose of ICS significantly increased the incidence of OC, compared with the lower dose group (RR = 2.48, 95% CI: 1.23 to 4.99, P = 0.011) under a fixed-effects model (heterogeneity: I^2 = 0.0%, P = 0.426) (**Figure 3**). Thereinto, RR of high-dose vs. middle-dose group was 4.00 (95% CI: 0.92 to 17.30), and was 2.10 (95% CI: 0.94 to 4.71) of middle-dose vs. low-dose group (**Figure 3**), suggesting risk of OC incidence was tied to ICS dose.

Comparison of OC incidence between ICS application groups with and without a spacer device: ICS application with a spacer device showed a significantly decreased incidence of OC, compared with that without the device (RR: 0.37, 95% CI: 0.22 to 0.63, P < 0.001) under a fixed-effects model (heterogeneity: I^2 = 43.2%, P = 0.134, **Figure 4**).

Only one study concerned the effect of different ICS types on OC incidence, and it found that on an equal dose, budesonide had a lower risk of OC than fluticasone; however, without statistical significance (RR: 0.62, 95% CI: 0.21 to 1.78, P = 0.38).

Combined OC incidence of patients receiving ICS in different study types: A total of 6644 patients prescribed with ICS were included and

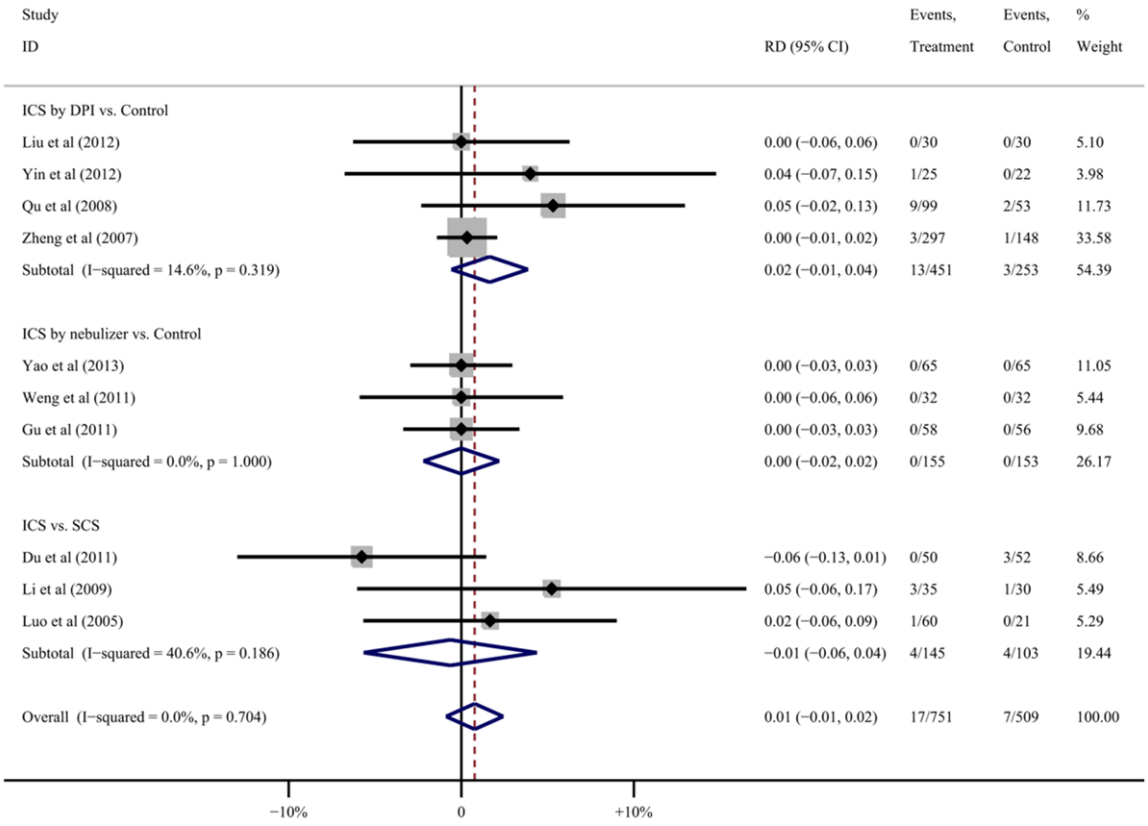

Figure 2. Forest plots of the effects on oral candidiasis incidence in the comparison of ICS vs. non-ICS. ICS: inhaled corticosteroid; RD: risk difference; CI: confidence interval; DPI: dry-powder ICS; SCS: systematic ICS.

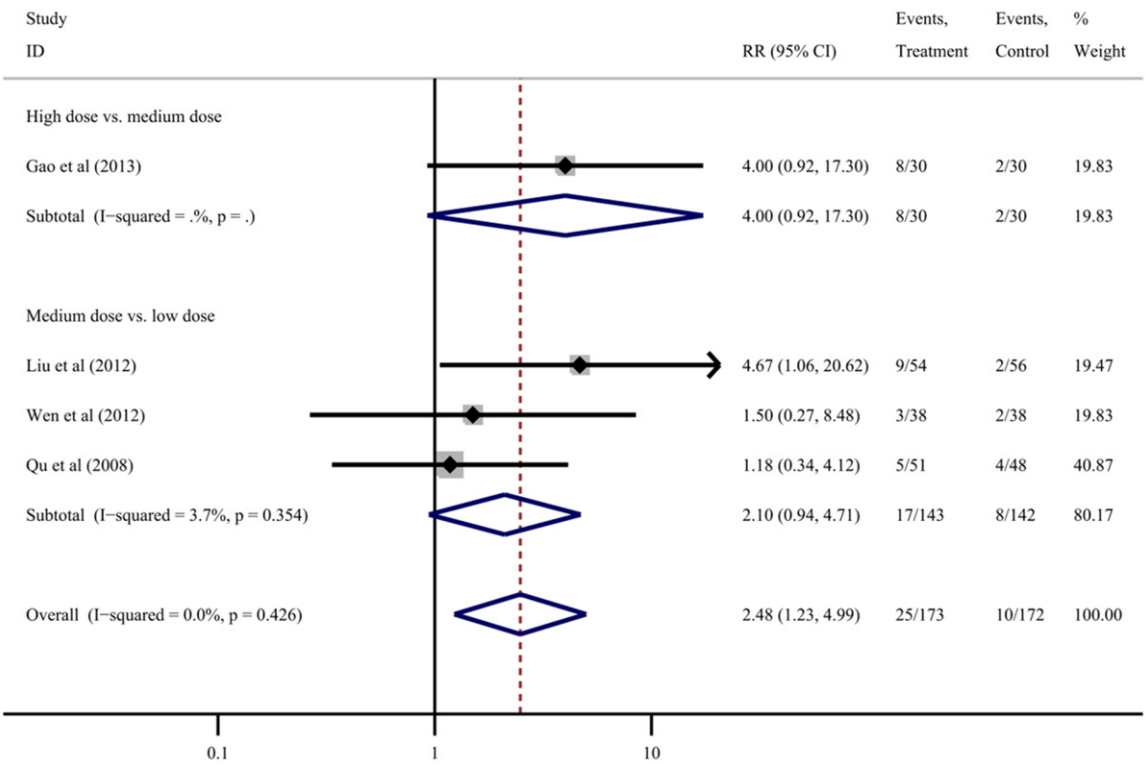

Figure 3. Forest plots of the effects on oral candidiasis incidence in the comparison of OC incidence between different ICS dose groups. ICS: Inhaled corticosteroid; RR: risk ratio; CI: confidence interval.

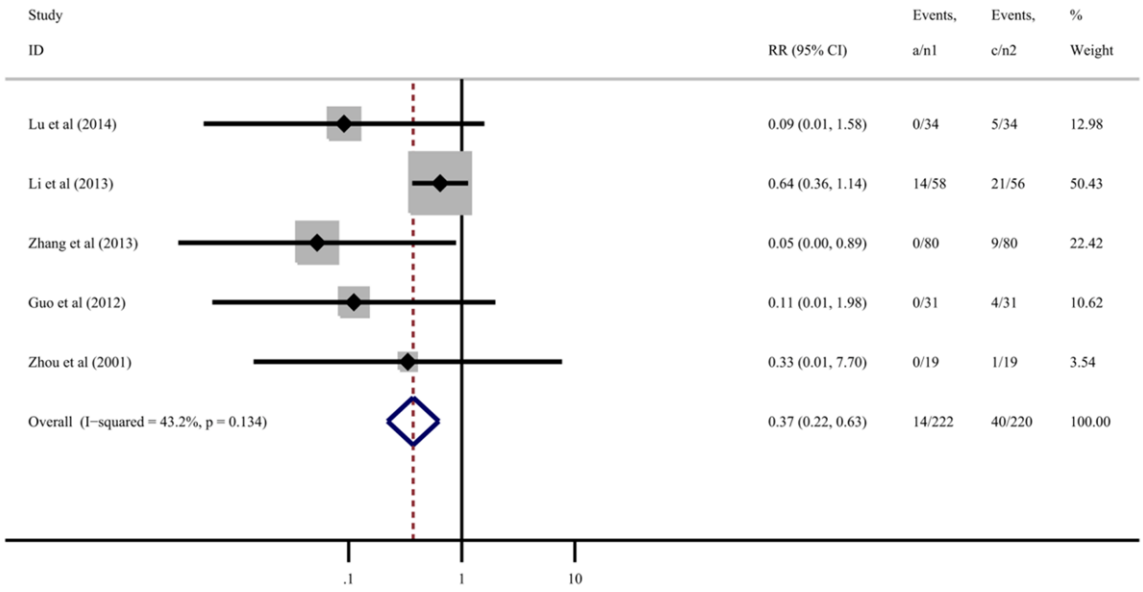

Figure 4. Forest plots of the effects on oral candidiasis incidence in the comparison of application of ICS with vs. without a spacer device. ICS: Inhaled corticosteroid; RR: risk ratio; CI: confidence interval.

the OC was detected in 419 of them. Oropharyngeal pathogens were collected from 943 patients receiving ICS, and 87 *Candida albicans* were detected after appropriate cultivation. After continuity correction, the overall incidence of OC was 5.1% (95% CI: 4.0% to 6.1%). In RCTs comparing influence of ICS and non-ICS, the incidence was 1.44% (95% CI: 0.4% to 2.4%, **Figure 5A**); and in RCTs comparing different ICS dosages, it was 10.0% (95% CI: 5.1% to 14.8%, **Figure 5B**); while in studies preventing OC after using ICS, it was 2.4% (95% CI: 1.1% to 3.7%, **Figure 5C**) and 16.4% (95% CI: 11.6%~21.2%, **Figure 5D**) in preventive treatment group and control group, respectively. In observational studies, OC incidence was 3.2% (95% CI: 1.9% to 4.5%, **Figure 5E**).

Overall detection rate of oropharyngeal candidiasis was 8.02% (95% CI: 5.03% to 11.00%), which was only reported in studies preventing ICS caused OC, and in trial group, it was 1.96% (95% CI: 0.76% to 3.15%), while in control group, it was 16.2% (95% CI: 12.8% to 19.7%) (**Figure 6**).

Publication bias

As shown in the funnel plot, there was no obvious dissymmetry in RCTs comparing OC incidence between using and not using ICS, and those between higher dose and lower dose, indicating a lack of publication bias of the selected articles (**Figure 7A** and **7B**). Egger's test also confirmed the result (P > 0.05). However, in the RCTs comparing ICS with and without a spacer device, there detected a significant publication bias (**Figure 7C**) (Egger's test: P = 0.032).

Discussion

In our study, we included a set of 46 articles to comprehensively evaluate the relationship between ICS and incidence of OC among Chinese patients. As a result, we found that there was no significant difference in OC incidence between ICS and non-ICS groups, regardless of the ICS devices (DPI or NI) in RCTs. However, in ICS application cases, the results suggested higher dose of ICS significantly resulted in a higher OC incidence, while the use of a spacer device significantly reduced the incidence.

With the advantages of local anti-inflammatory activity and minor systematic adverse effect, ICS has been widely used for asthma and COPD treatment [60]. However, more and more studies have reported the increased risk of OC after this application [61], which reduces the compliance with ICS. Boven and Vegter performed a sequence symmetry analysis through retrieving the IADB, and found that after 1 year of ICS ini-

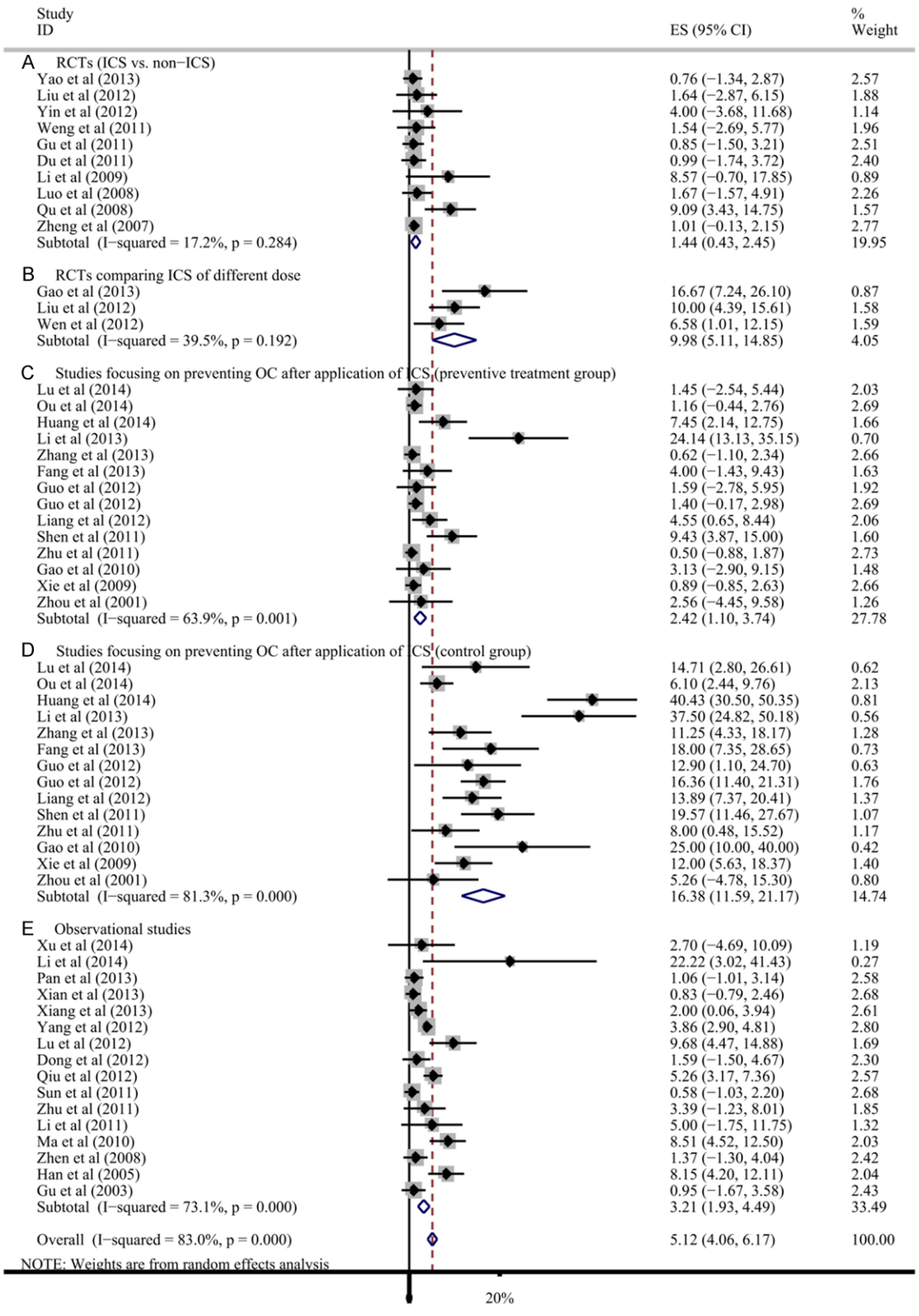

Figure 5. Oral candidiasis (OC) incidences in different study types. A: In RCTs of ICS vs. non-ICS; B: RCTs comparing ICS of different dose; C: In studies focusing on preventing OC incidence after application of ICS (preventive treatment group); D: In studies focusing on preventing OC incidence after application of ICS (control group); E: Observational studies. RCT: randomized controlled trial; ICS: Inhaled corticosteroid; ES: estimate; CI: confidence interval.

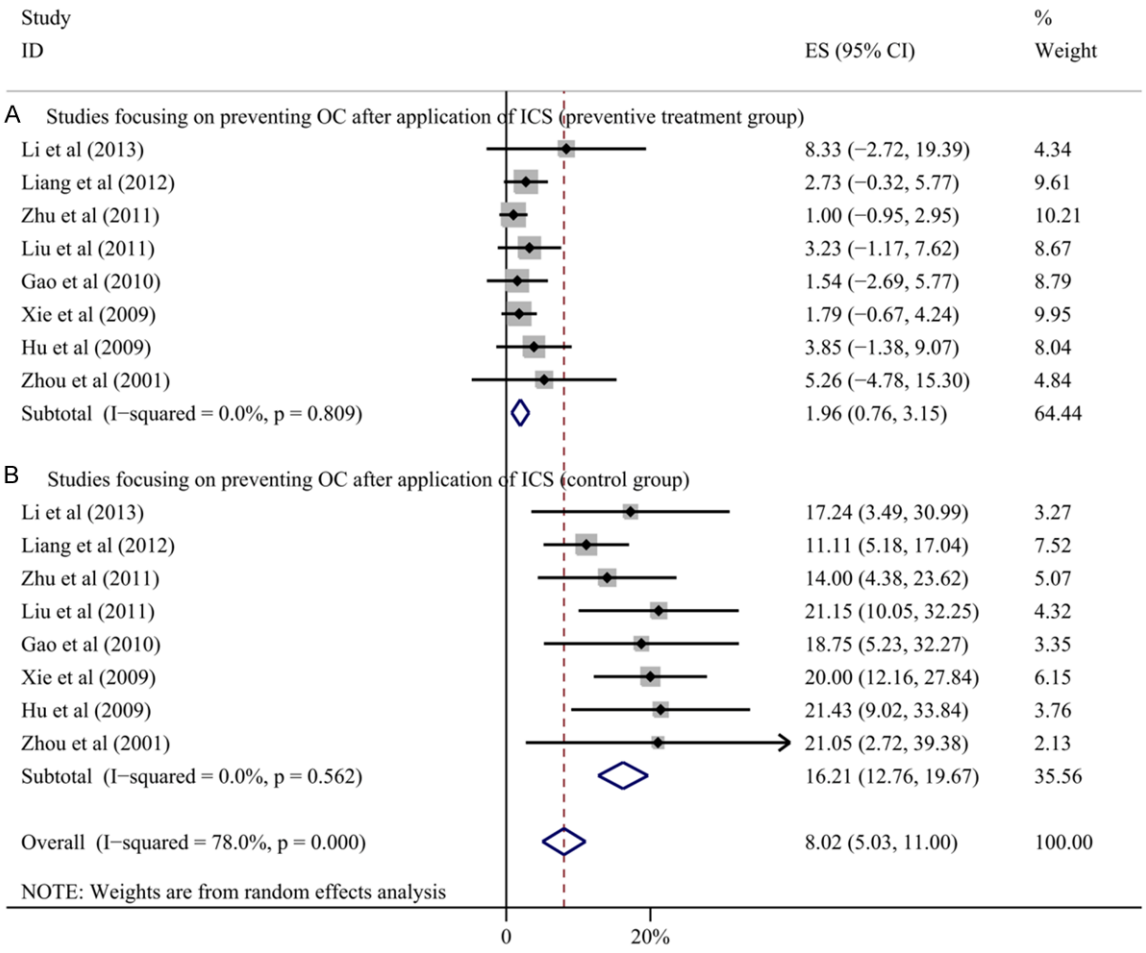

Figure 6. Detection rate of oropharyngeal candidiasis. A: Studies focusing on preventing OC after application of ICS (preventive treatment group); B: Studies focusing on preventing OC after application of ICS (control group).

tiation, 701 patients received medication for OC, whereas 1 year before the administration, only 361 patients received the medications, thus the sequence ration (SR) was 1.94 (95% CI: 1.71 to 2.21) [3], indicating an increased risk of OC after 1 year of ICS initiation. Another Canadian case-control study indicates that 3-year incidence of OC in patients prescribed with ICS is 7.3% (1891/25762), and higher ICS dose is significantly associated with increased risk of OC [61]. In addition, a previous meta-analysis containing 23 RCTs revealed that occurrence of OC in ICS group was 3.92%, significantly higher than the placebo control (OR = 3.57, P < 0.001). Moreover, compared with placebo control, the higher dose of ICS was significantly associated with the greater risk of OC (beclomethasone dipropionate: OR = 13.64, P = 0.08; fluticasone propionate: OR = 4.51, P = 0.01) [6]. Although mechanisms of how ICS could cause OC occurrence has not been defined, the deposition of ICS in the oropharyngeal cavity can result in OC [62]. It is proposed that the decreased local immunity such as inhibition of normal host defense functions at the oral mucosal surface, and the increased salivary glucose level, can lead to the occurrence of OC [63].

This is the first meta-analysis combining eligible studies to ascertain the adverse effect of ICS on OC among Chinese patient, and the result would provide a novel insight into the relationship between ICS and OC. Inconsistent with previous findings, in the present study, we did not observe a significant association between ICS and OC incidence in comparison with non-ICS, which might due to the potent preventive action and strict threshold for OC identification. On the other hand, our result also showed

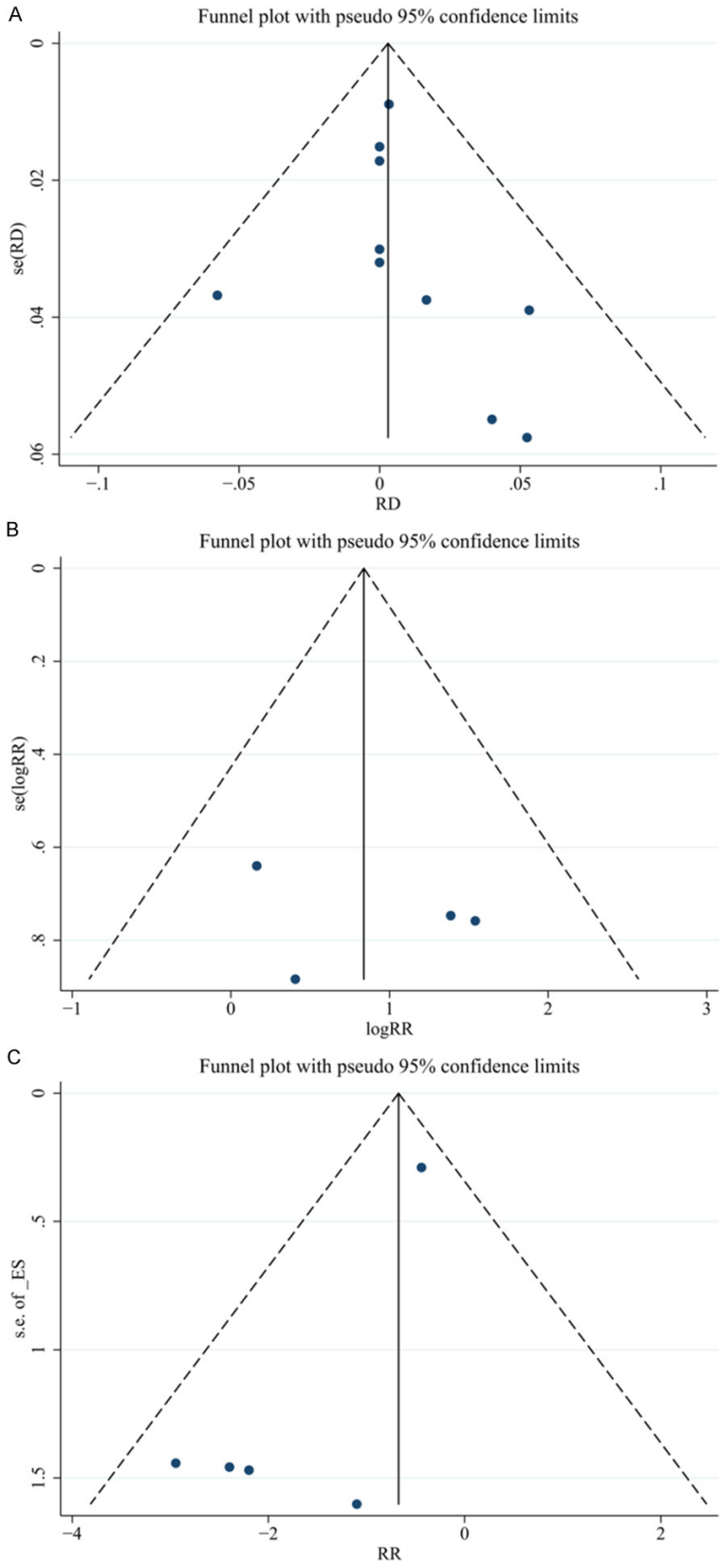

Figure 7. Funnel plots of the included studies in different comparisons. A: ICS vs. non-ICS; B: Higher dose vs. lower dose; C: ICS with vs. without a spacer device. ICS: Inhaled corticosteroid; RD: Risk difference; RR: Risk ratio.

that higher dose of ICS posed a significant higher OC incidence, whereas ICS application with a spacer device posed a significant lower OC incidence, which was in accordance with the previous study [6].

Furthermore, we examined the OC incidence in different study types, and found different results, suggesting that the observed incidence was varied depending on different comparisons and study aims. Other factors such as prevention method were different in different study types, and this might explain the different incidences. In studies focused on preventing OC, the preventive group achieved a decreased incidence than control group (2.4% vs. 16.4%), providing evidence that proper preventive actions would reduce the OC incidence, such as mouth wash and oral care. In studies evaluating ICS efficiency, most of the researchers have taken active prevention actions to guarantee good efficiency and reduce adverse effect, thus resulted in a lower incidence than other study types. Moreover, diagnostic sensitivity might be another confounding factor. Several OC patients only have signs of mucosa hyperemia and leukoplakia, but not obvious symptom. Those signs were not remarkable. Therefore, the OC detection is depending on the researchers' experience and concern degree. In studies focused on adverse effects of ICS, researchers would have a careful examination on mouth mucosa, and resulted in a higher diagnostic sensitivity. By contrast, in observational

studies, most of the OC cases were diagnosed according to patients' oral reports, and this might cause a relatively lower diagnostic sensitivity and accuracy. Therefore, it is understandable that the OC incidence was higher in control group in studies focused on preventing OC (16.4%) and the RCTs comparing different ICS dosages (10.0%) than the observational studies (3.2%).

Although our study provided a comprehensive evaluation of associations between ICS and OC among Chinese patients, there were several limitations. First, most of the included studies did not mention the random selection method, or conceal allocation or blind method, which might influence the result. Moreover, in the analysis regarding the influence of spacer device, obvious publication bias was detected, suggesting a deviation of the result. Nevertheless, this study is of great value in the revelation of adverse effect of ICS application on OC among Chinese patients.

In conclusion, in Chinese patients higher dose of ICS had a significantly increased incidence of OC, and ICS application with a spacer device had a significant lower OC incidence. OC incidence might be reduced by several prevention measures. ICS was not significantly associated with OC incidence given appropriate prevention.

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Disclosure of conflict of interest

None.

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