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# BMJ Open

## **Efficacy and safety of omalizumab in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis of randomized controlled trials**

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4 **Efficacy and safety of omalizumab in chronic rhinosinusitis with nasal polyps:**  
5  
6 **a systematic review and meta-analysis of randomized controlled trials**  
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## Abstract

### Objectives

To assess the efficacy and safety of omalizumab for chronic rhinosinusitis with nasal polyps (CRSwNP) and to identify evidence gaps that will guide future research on omalizumab for CRSwNP.

### Design

Systematic review and meta-analysis.

### Methods

A comprehensive search was performed in Pubmed, Embase, Web of Science, and the Cochrane Library on 13 October 2020. Two independent authors screened search results, extracted data and appraised studies using the Cochrane risk of bias tool. Only randomized controlled trials (RCTs) assessing omalizumab in adult patients for CRSwNP were included.

### Results

A total of 4 RCTs involving 303 participants were identified. When comparing omalizumab to placebo, there was a significant difference in nasal polyps score (mean difference (MD) = -1.11; 95% confidence interval (CI), -2.09 to -0.13), nasal congestion score (MD = -0.78; 95% CI, -1.25 to -0.30), Sino-Nasal Outcome Test-22 (MD = -15.62; 95% CI, -19.79 to -11.45), Total Nasal Symptom Score (MD = -1.84; 95% CI, -2.43 to -1.25), and reduced need for surgery (risk ratio (RR) = 5.61; 95% CI, 1.99 to 15.81). Furthermore, there was no difference in the risk of serious adverse

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4 events ((RR = 1.40; 95% CI, 0.29 to 6.80), adverse events (RR = 0.83; 95% CI, 0.60 to  
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7 1.15) and rescue systemic corticosteroid (RR = 0.52; 95% CI, 0.17 to 1.61).

## 9 **Conclusions**

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11  
12 This was the first meta-analysis that identified omalizumab significantly improved  
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15 endoscopic, clinical, and patient-reported outcomes in adults with moderate to severe  
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18 CRSwNP and it was safe and well-tolerated.

## 20 **PROSPERO registration number**

21  
22  
23 CRD42020207639.

24  
25  
26 **Keywords:** omalizumab; anti-IgE antibody; chronic rhinosinusitis; nasal polyps;  
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28 systematic review; meta-analysis

## 30 **Strengths and limitation of this study**

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33  
34 1. Omalizumab, an anti-IgE antibody, is a novel treatment for CRSwNP. However, its  
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37 efficacy and safety are not well known.
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40 2. In this systematic review and meta-analysis, we identified that omalizumab improved  
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43 health-related quality of life and reduced the extent of the disease and the need for  
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46 surgery in adults with moderate to severe CRSwNP and it was safe.
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49 3. Studies are required to evaluate their effectiveness in patients with less severe  
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52 diseases and their cost in the treatment.
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## Introduction

Chronic rhinosinusitis (CRS) is common and affects up to 5-12% of the general population<sup>1</sup>. It is defined as inflammation of the nose and the paranasal sinuses characterized by nasal congestion, nasal discharge, facial pressure, and loss of smell. CRS with nasal polyps (CRSwNP) is a severe form of CRS and accounts for 18% of patients with CRS<sup>2</sup>. CRSwNP is associated with adult-onset asthma, decreased health-related quality of life (HRQoL)<sup>3, 4</sup>, and substantial economic burden<sup>5</sup>. Many patients with CRSwNP often fail to achieve sufficient benefit from intranasal corticosteroids (INCS) or systemic corticosteroids (SCS) and/ or functional endoscopic sinus surgery (FESS)<sup>6</sup>. Although FESS may be successful initially, relapse occurs in 20% of patients after 12 months<sup>7</sup>, in 40% after 18 months<sup>8</sup>, and in 80% after 12 years despite ongoing INCS therapy<sup>9</sup>. Therefore, novel treatments such as biologics are needed for CRSwNP. Omalizumab (anti-IgE antibody) is one of the biologics and may help patients with severe CRSwNP. It was reported that omalizumab made their symptom better and shrank their polyps in small-size randomized controlled trials (RCTs)<sup>10, 11</sup>. But some of its effectiveness and safety are not well known. Thus, some systematic reviews were conducted to assess the effectiveness and safety of it. But they found very little information or insufficient evidence about the use of omalizumab and cannot determine whether it was effective or not<sup>12, 13</sup>. Currently, some well-designed RCTs about omalizumab for CRSwNP were published<sup>14</sup>, which may provide us with some evidence. Therefore, this systematic review was conducted to evaluate the efficacy and safety of

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4 omalizumab versus placebo in adult patients with CRSwNP, and identify evidence gaps  
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7 that will guide future research on omalizumab for CRSwNP.  
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## 10 **Methods**

11  
12 We performed a systematic review based on a priori protocol that was registered with  
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14 PROSPERO (No. CRD42020207639)<sup>15</sup>. This review was reported according to the  
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16 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)  
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18 statement<sup>16</sup> (Additional file 1).  
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## 23 **Eligibility criteria**

24  
25 (a) Population: adult patients (>18) with CRSwNP; (b) Intervention and comparison:  
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27 studies comparing omalizumab with placebo, given for at least 16 weeks; (c) Study  
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29 design: randomized controlled trials (RCTs); (d) Studies written and published in the  
30  
31 English language were included.  
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## 36 **Search strategy and selection process**

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38 A comprehensive search was performed in Pubmed, Embase, Web of Science, and the  
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40 Cochrane Library on 13 October 2020. We used the following combined text and  
41  
42 MeSH terms: “nasal polyps”, “sinusitis” and “omalizumab”. Search strategies for major  
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44 databases are provided in Appendix 1.  
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50 Titles and abstracts of the retrieved articles were then screened for their potential  
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52 relevance by two reviewers (Q.W Wu and L.X Yuan ). The full-text articles were  
53  
54 obtained and assessed by the same reviewers to determine whether they met the  
55  
56 inclusion criteria for this review. We resolved any differences by a discussion with a  
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4 third author (Q.T Yang).  
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### 6 7 **Data extraction**

8  
9 Two reviewers (H.J Qiu and X.Y Wang) read full-text articles and extracted data using  
10  
11 a pre-defined extraction form. Data were extracted on the following: first author, year  
12  
13 of publication, patient characteristics, study methods, and outcome data.  
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### 17 18 **Assessment of risk of bias**

19  
20 In this review, the original version of the Cochrane 'Risk of bias' tool was used to assess  
21  
22 the risk of bias in included studies. The risk of bias was assessed as 'low', 'high' or  
23  
24 'unclear' for each of the following six domains: sequence generation; allocation  
25  
26 concealment; blinding of participants, personnel and outcome assessment; incomplete  
27  
28 outcome data; selective reporting; other sources of bias (if required).  
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### 33 34 **Statistical analysis**

35  
36 Study characteristics were shown in tables and described narratively. All meta-analyses  
37  
38 were conducted by Review Manager (version 5.3). For dichotomous data, we planned  
39  
40 to analyze treatment differences as a risk ratio (RR) calculated using the Mantel-  
41  
42 Haenszel methods. For continuous outcomes, we planned to express treatment effects  
43  
44 as a mean difference (MD) with standard deviation (SD) or as a standardized mean  
45  
46 difference (SMD) if different scales had been used to measure the same outcome.  
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52 Statistical heterogeneity was assessed by the Chi<sup>2</sup> test (with a significance level set at  
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54 P value < 0.10) and the I<sup>2</sup> statistic. A random-effects model was used in the analysis if  
55  
56 it was likely heterogeneity. The possibility of publication bias was assessed by  
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4 constructing a funnel plot if sufficient studies ( $> 10$ ) were available for an outcome.  
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## 7 **Results**

### 8 **Study selection**

9  
10 We identified 1966 articles, of which 3 (with data for 302 participants) were included  
11  
12 in our analysis (Figure 1). The 3 articles (Pinto 2010<sup>10</sup>, Gevaert 2013<sup>11</sup>, and Gavaert  
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14 2020<sup>14</sup>) were published between 2010 and 2020, of which Gavaert 2020 reported 2  
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16 RCTs (POLYP1 2020 and POLYP2 2020).  
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### 23 **Study characteristics**

24  
25 A summary of key participant characteristics, interventions, and comparison pairs was  
26  
27 shown in Table 1. Except for 2 participants in Pinto 2010, all the participants were  
28  
29 adults with CRSwNP. All the studies were double-blind RCTs and used a placebo.  
30  
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33  
34 Study duration ranged from 20 weeks to 26 weeks.  
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36

### 37 **Risk of bias and quality of the clinical trials**

38  
39 There were 4 RCTs included in this review. Overall the risk of bias was low, except the  
40  
41 random sequence generation of Pinto 2010 was unclear. Our judgments about each risk  
42  
43 of bias item presented as percentages across all included studies were shown in Figure  
44  
45  
46  
47 2. Our judgments about each risk of bias item for each included study were shown in  
48  
49  
50  
51 Figure 3.  
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### 53 **Primary outcomes**

54  
55 The mean difference (MD) in the change of nasal polyps score (NPS) was -1.11 (95%  
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57 confidence interval (CI), -2.09 to -0.13; 4 RCTs; 302 participants;  $I^2 = 90\%$ ; Figure  
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4 4A). We noted the high  $I^2$  value and Pinto 2020 had no significant reduction in NPS.  
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6  
7 However, the removal of Pinto 2020 did not change the overall effect size in sensitivity  
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9  
10 analyses. Therefore, we considered the certainty of the evidence to be high despite the  
11  
12 large  $I^2$  value.

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15 The pooled mean difference of nasal congestion score (NCS ) is -0.78 favoring the  
16  
17 groups receiving omalizumab (95% CI, -1.25 to -0.30; 3 RCTs; 288 participants;  $I^2 =$   
18  
19 82%; Figure 4B). Although the heterogeneity was high in this analysis, all 3 RCTs  
20  
21 showed a significant reduction in NCS with omalizumab.  
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25  
26 The Sino-Nasal Outcome Test-22 (SNOT-22) score was 15.62 points lower in  
27  
28 participants who received omalizumab (MD = -15.62; 95% CI, -19.79 to -11.45; 265  
29  
30 participants;  $I^2 = 0%$ ; Figure 4C). Because the different measuring tools (Pinto 2010,  
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32 SNOT-20; Gevaert 2013, Short-Form Health Questionnaire (SF-36)) and unavailable  
33  
34 data , these 2 RCTs were excluded in this pooled analysis.  
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### 38 39 **Secondary outcomes**

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42 The mean difference in the change of Total Nasal Symptom Score (TNSS) was 1.84  
43  
44 points lower in omalizumab group (MD = -1.84; 95% CI, -2.43 to -1.25; 3 RCTs; 279  
45  
46 participants;  $I^2 = 0%$ ; Figure 4D).  
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49  
50 No serious adverse events (SAEs) were reported in Gevaert 2013 and Pinto 2010.  
51  
52  
53 However, POLYP1 2020 reported 1 case in the placebo group with myocardial  
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55 infarction and POLYP2 2020 reported 1 case of pneumonia in the placebo group and 3  
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57 cases in the omalizumab group (1 snake bite, 1 hand fracture, and 1 asthma  
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4 exacerbation). The pooled result indicated that there was no difference in the risk of  
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6 SAEs (risk ratio (RR) = 1.40; 95% CI, 0.29 to 6.80; 4 RCTs; 302 participants;  $I^2 = 28\%$ ;  
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8 Figure 4E).

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11  
12 There was no difference in the risk of adverse events (AEs) (RR = 0.83; 95% CI, 0.60  
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14 to 1.15; 4 RCTs; 302 participants;  $I^2 = 0\%$ ; Figure 4F). It was uncertain where or not  
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16 there was a difference in the risk of rescue systemic corticosteroid (RSCS; RR = 0.52;  
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18 95% CI, 0.17 to 1.61; 3 RCTs; 279 participants;  $I^2 = 0\%$ ; Figure 4G). POLYP1 2020  
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20 and POLYP2 2020 reported the number of reduced need for surgery (RNS). The  
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22 proportion was higher in the group that received omalizumab (RR = 5.61; 95% CI, 1.99  
23  
24 to 15.81; 2 RCTs; 265 participants;  $I^2 = 0\%$ ; Figure 4H).

## 31 Discussion

### 33 Principal findings

34  
35 This systematic review and meta-analysis identified 4 RCTs with 302 participants  
36  
37 evaluating the efficacy and safety of omalizumab in CRSwNP. It showed that  
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39 omalizumab significantly improved the size of nasal polyps (measured by NPS),  
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41 symptoms (measured by NCS and TNSS), and Health-related quality of life (HRQoL;  
42  
43 measured by SNOT-22), and reduce the need for surgery (measured by RNS). What's  
44  
45 more, there was no difference in the risk of SAEs, AEs, and RSCS.

### 53 Comparison with other studies

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55 Hong included two studies (Gavaert 2013 and Pinto 2010) and made a narrative  
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57 systematic review<sup>12</sup>. They concluded that there was insufficient evidence to determine  
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4 the effectiveness of omalizumab for CRS. In Chong's systematic review and meta-  
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6 analysis, there were 3 small studies with 65 participants (Gavaert 2013, Pinto 2010, and  
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8 NCT01066104) evaluated omalizumab<sup>13</sup>. Their results also showed that there were very  
9  
10 uncertain about the effect of omalizumab on disease-specific HRQoL, severe adverse  
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12 events, the extent of disease (CT scan scores), generic HRQoL, and adverse effects.  
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15 NCT01066104<sup>17</sup> included in Chong's review was unpublished data, so it was excluded  
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18 in our study according to our inclusion criteria.  
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### 22 23 **Implication for future research and clinical practice**

24  
25 Patients with CRSwNP and comorbid asthma often have a high symptom burden,  
26  
27 substantial impact on HRQoL, and a higher risk of RSCS and revision surgery<sup>1</sup>. There  
28  
29 were 4 RCTs included in this systematic review, which recruited patients with moderate  
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31 to severe CRSwNP. The patients in omalizumab group experienced significant  
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33 improvements in HRQoL, and reduced disease severity and need for surgery.  
34  
35 Furthermore, there was no increased risk of SAEs and AEs in patients treated with  
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37 omalizumab. Thus, it was certain that omalizumab significantly improved endoscopic,  
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39 clinical, and patient-reported outcomes in moderate to severe CRSwNP and it was well  
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41 tolerated.  
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50 However, it is still unknown that omalizumab is effective in patients with less severe  
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52 disease and more affordable compared to conventional treatment with topical and  
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54 systemic corticosteroids and surgery. Therefore, studies are required to evaluate their  
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56 effectiveness in patients with less severe diseases and their cost in the treatment. In  
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4 addition, long-term observational studies are also required to determine if omalizumab  
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7 lose its effectiveness over time, or whether there are any late adverse events.  
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### 9 **Limitations of the study**

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12 Despite the strict methodology of this systematic review and meta-analysis using  
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14 PRIMSA guidelines, certain limitations should be considered. First, studies recruited  
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16 participants with moderate to severe CRSwNP, as half of participants also had asthma  
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18 as comorbidity or inhaled asthma therapy. Therefore, there is no evidence on whether  
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20 or not patients with less severe disease (without asthma) would benefit. Secondly, 4  
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22 RCTs were all in adults and no available data for children. Thirdly, because the longest  
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24 follow-up of 4 RCTs was only up to 26 weeks, there were too short to comprehensively  
25  
26 and adequately assess the risks of side effect, RSCS, and RNS. Finally, there were only  
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28 4 RCTs (<10), so a possibility of publication bias was not assessed by constructing a  
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30 funnel plot in this systematic review<sup>18</sup>.  
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### 39 **Conclusions**

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42 To the best of our knowledge, this was the first meta-analysis that identified  
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44 omalizumab significantly improved endoscopic, clinical, and patient-reported  
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46 outcomes in moderate to severe CRSwNP and it was safe and well-tolerated. Studies  
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48 are required to evaluate their effectiveness in patients with less severe diseases and their  
49  
50 cost in the treatment.  
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60 N/A.

## Contributors

Concept and design: R Zheng and Q.T Yang. Acquisition, analysis, or interpretation of data: Q.W Wu, L.X Yuan, Q.H Qiu, X.Y Wang, and X.K Huang. Drafting of the manuscript: QW Wu and L.X Yuan. Critical revision of the manuscript for important intellectual content: R Zheng and Q.T Yang. Statistical analysis: L.X Yuan. Supervision: R Zheng and Q.T Yang.

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## Competing interests

No potential conflict of interest was reported by the authors.

## Patient consent for publication

Not required.

## Provenance and peer review

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4 Not commissioned; externally peer reviewed.  
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8 **Data availability statement**  
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11 All data relevant to the study are included in the article or uploaded as supplementary  
12  
13 information.  
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**Appendix 1. Search strategies**

<b>Pubmed</b>
1. nasal polyps[MeSH Terms]
2. (((nasal polyp*[Title/Abstract]) OR (nasal papilloma[Title/Abstract])) OR (nose polyp*[Title/Abstract])) OR (nasi papilloma[Title/Abstract])) OR (nasi polyposis[Title/Abstract])
3. #1 OR #2
4. sinusitis[MeSH Terms]
5. ((((((chronic rhinosinusitis[Title/Abstract]) OR (rhinopolyp*[Title/Abstract])) OR (CRSwNP[Title/Abstract])) OR (sinus Infection*[Title/Abstract])) OR (rhinitis[Title/Abstract])) OR (pansinusitis[Title/Abstract])) OR (sphenoid* sinusitis[Title/Abstract])
6. #4 OR #5
7. omalizumab[MeSH Terms]
8. (((Xolair[Title/Abstract]) OR (anti-IgE antibody[Title/Abstract])) OR (anti-IgE monoclonal antibody[Title/Abstract])) OR (anti-IgE mAb[Title/Abstract])
9. #7 OR #8
10. #3 OR #6
11. #9 AND #10
<b>Cochrane Library</b>
1. MeSH descriptor: [Nasal Polyps] explode all trees
2. (nasal polyp*):ti,ab,kw OR (nasal papilloma):ti,ab,kw OR (nose polyp*):ti,ab,kw OR (nasi papilloma):ti,ab,kw OR (nasi polyposis):ti,ab,kw (Word variations have been searched)
3. #1 OR #2
4. MeSH descriptor: [Sinusitis] explode all trees
5. (chronic rhinosinusitis):ti,ab,kw OR (rhinopolyp*):ti,ab,kw OR (CRSwNP):ti,ab,kw OR (sinus infection*):ti,ab,kw OR (rhinitis):ti,ab,kw (Word variations have been searched)
6. #4 OR #5
7. (pansinusitis):ti,ab,kw OR (sphenoid* sinusitis):ti,ab,kw (Word variations have been searched)
8. #6 OR #7
9. MeSH descriptor: [Omalizumab] explode all trees
10. (Xolair):ti,ab,kw OR (anti-IgE antibody):ti,ab,kw OR (anti-IgE monoclonal antibody):ti,ab,kw OR (anti-IgE mAb):ti,ab,kw (Word variations have been searched)
11. #9 OR #10
12. #3 OR #8
13. #11 AND #12
<b>Embase</b>

1. 'nose polyp'/exp
2. 'nasal polyp\*' OR 'nasal papilloma'/exp OR 'nasal papilloma' OR 'nose polyp\*' OR 'nasi papilloma' OR 'nasi polyposis':ab,ti
3. #1 OR #2
4. 'sinusitis'/exp
5. 'chronic rhinosinusitis rhinopolyp\*' OR crswnp OR 'sinus infection\*' OR rhinitis OR pansinusitis OR 'sphenoid\* sinusitis':ab,ti
6. #4 OR #5
7. #3 OR #6
8. 'omalizumab'/exp
9. 'xolair' OR 'anti-ige antibody' OR 'anti-ige monoclonal antibody' OR 'anti-ige mab':ab,ti
10. #8 OR #9
11. #7 AND #10
12. #7 AND #10 AND [medline]/lim
13. #11 NOT #12

#### Web of Science

1. TOPIC: (nasal polyp\*) OR TOPIC: (nasal papilloma) OR TOPIC: (nose polyp\*) OR TOPIC: (nasi papilloma) OR TOPIC: (nasi polyposis)
2. TOPIC: (sinusitis) OR TOPIC: (chronic rhinosinusitis) OR TOPIC: (rhinopolyp\*) OR TOPIC: (CRSwNP) OR TOPIC: (sinus Infection\*) OR TOPIC: (rhinitis) OR TOPIC: (pansinusitis) OR TOPIC: (sphenoid\* sinusitis)
3. #1 OR #2
4. TOPIC: (omalizumab) OR TOPIC: (Xolair) OR TOPIC: (anti-IgE antibody) OR TOPIC: (anti-IgE monoclonal antibody) OR TOPIC: (anti-IgE mAb)
5. #3 AND #4

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4 **Table 1.** Summary of characteristics of included RCTs  
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6 **Figure 1.** PRISMA flow diagram of the literature search.  
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9 **Figure 2.** ‘Risk of bias’ graph: review authors’ judgements about each risk of bias item  
10 presented as percentages across all included studies.  
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14 **Figure 3.** ‘Risk of bias’ summary: review authors’ judgements about each risk of bias  
15 item for each included study.  
16  
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18  
19 **Figure 4.** Meta-analyses of omalizumab versus placebo, comparing efficacy and safety.  
20  
21 Outcomes assessed are: (A) Nasal polyps score (NPS); (B) Nasal congestion score  
22 (NCS); (C) Sino-Nasal Outcome Test-22 (SNOT-22); (D) Total nasal symptom score  
23 (TNSS); (E) Serious adverse events (SAEs); (F) Adverse events (AEs); (G) Rescue  
24 systemic corticosteroid (RSCS) and (H) Reduced need for surgery (RNS).  
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**Table 1.** Summary of characteristics of included RCTs

Study, year	Population	Comorbidity	Omalizumab*	Placebo	Treatment length	Follow-up length	Age (y), mean (SD)		Male, no.(%)	
							Omalizumab	Placebo	Omalizumab	Placebo
Pinto 2010 <sup>10</sup> (n = 14)	CRSwNP (all had undergone endoscopic sinus surgery)	inhaled asthma therapy (72% (5/7) in omalizumab group and 43% (3/7) in placebo group)	subcutaneously	injection, same dose and frequency	26 weeks	26 weeks	43.1 (9.8)	48.6 (9.1)	3 (43%)	7 (100%)
Gevaert <sup>11</sup> 2013 (n = 24)	CRSwNP	asthma (100%)	subcutaneously	injection, same dose and frequency	16 weeks	20 weeks	50 (44-56) <sup>#</sup>	45 (42-54) <sup>#</sup>	12 (80%)	4 (50%)
POLYP1 <sup>14</sup> 2020 (n = 138)	CRSwNP	asthma (58.3% (42/72) in omalizumab group and 48.5% (32/66) in placebo group)	subcutaneously	injection, same dose and frequency	24 weeks	24 weeks	50.0 (14.5)	52.2 (11.6)	47 (65.3)	41 (62.1)
POLYP2 <sup>14</sup> 2020 (n = 127)	CRSwNP	asthma (61.3% (38/62) in omalizumab group and 60% (39/65) in placebo group)	subcutaneously	injection, same dose and frequency	24 weeks	24 weeks	49.0 (11.9)	51.0 (12.0)	39 (62.9)	44 (67.7)

\*omalizumab subcutaneously (every 2 week or every month injections), based on total serum IgE levels and body weight, with a maximum dose of 375 mg; <sup>#</sup>mean (interquartile range, IQR); CRSwNP: chronic rhinosinusitis with nasal polyps; RCTs: randomized controlled trials; SD: standard deviation.

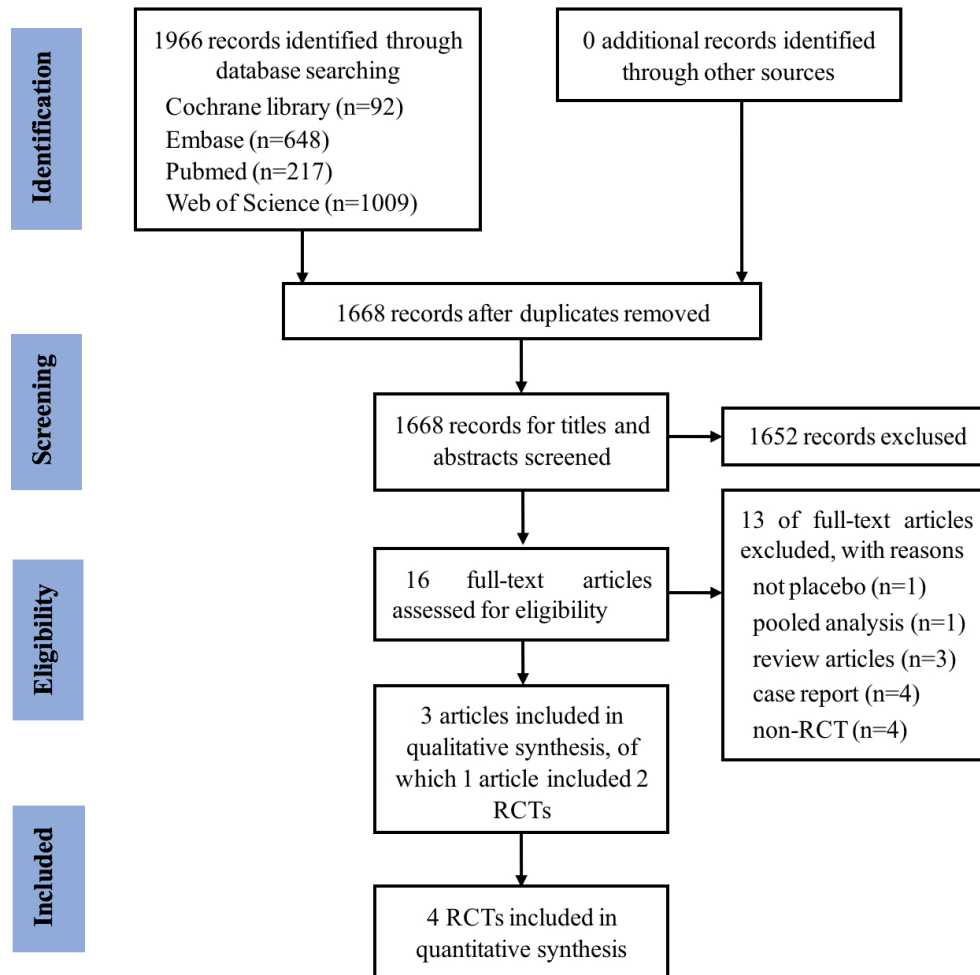


Figure 1. PRISMA flow diagram of the literature search.

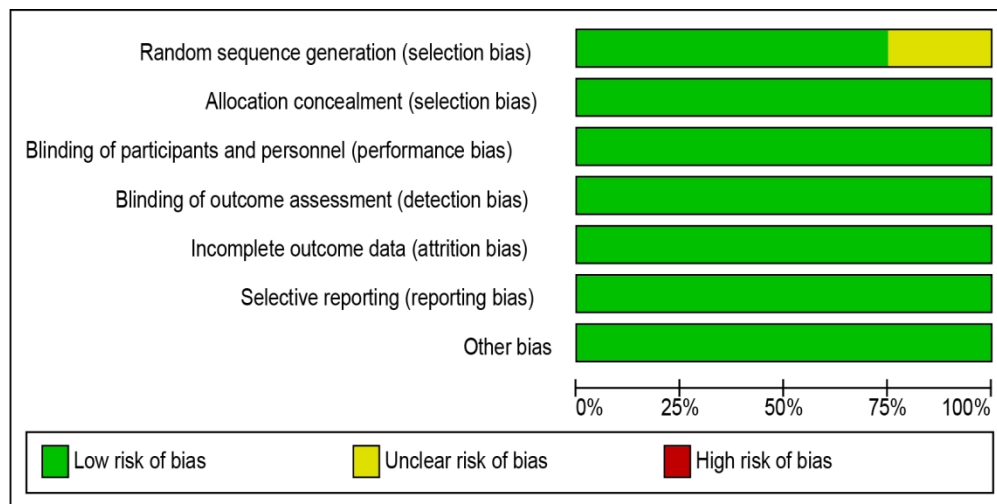


Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gevaert 2013	+	+	+	+	+	+	+
Pinto 2010	?	+	+	+	+	+	+
POLYP1 2020	+	+	+	+	+	+	+
POLYP2 2020	+	+	+	+	+	+	+

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

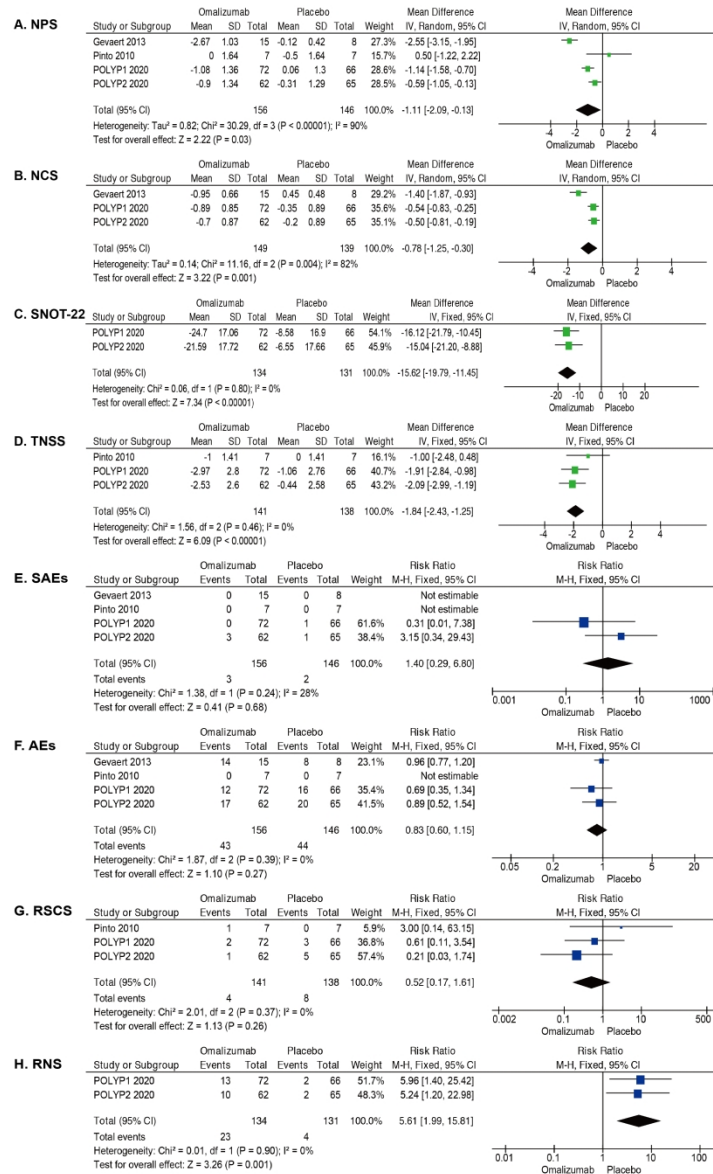


Figure 4. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Nasal polyps score (NPS); (B) Nasal congestion score (NCS); (C) Sino-Nasal Outcome Test-22 (SNOT-22); (D) Total nasal symptom score (TNSS); (E) Serious adverse events (SAEs); (F) Adverse events (AEs); (G) Rescue systemic corticosteroid (RSCS) and (H) Reduced need for surgery (RNS).



# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis.	6



# PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7; Figure 2 and 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-9; Figure 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9; Figure 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12



# PRISMA 2009 Checklist

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Page 2 of 2

For peer review only

# BMJ Open

## Efficacy and safety of omalizumab in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis of randomized controlled trials

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-047344.R1
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Date Submitted by the Author:	27-Mar-2021
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<b>Primary Subject Heading</b>:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Ear, nose and throat/otolaryngology
Keywords:	Adult otolaryngology < OTOLARYNGOLOGY, Endoscopic surgery < OTOLARYNGOLOGY, Adverse events < THERAPEUTICS, Clinical trials < THERAPEUTICS

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1 **Efficacy and safety of omalizumab in chronic rhinosinusitis with nasal polyps:**  
2 **a systematic review and meta-analysis of randomized controlled trials**

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4     20    **Abstract**

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7     21    **Objectives**

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9     22    To assess the efficacy and safety of omalizumab for chronic rhinosinusitis with nasal  
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12    23    polyps (CRSwNP) and to identify evidence gaps that will guide future research on  
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15    24    omalizumab for CRSwNP.

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17    25    **Design**

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20    26    Systematic review and meta-analysis.

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23    27    **Data Sources**

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26    28    A comprehensive search was performed in PubMed, Embase, Web of Science, and the  
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29    29    Cochrane Library on 13 October 2020.

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31    30    **Eligibility Criteria**

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34    31    Randomized controlled trials (RCTs) comparing omalizumab with placebo, given for  
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37    32    at least 16 weeks in adult patients with CRSwNP.

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39    33    **Data extraction and synthesis**

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42    34    Two independent authors screened search results, extracted data and assessed studies  
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45    35    using the Cochrane risk of bias tool. Data were pooled using the inverse-variance  
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48    36    method and expressed as mean differences (MDs) with 95% CIs. Heterogeneity was  
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51    37    assessed by the Chi<sup>2</sup> test and the I<sup>2</sup> statistic.

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53    38    **Results**

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56    39    A total of 4 RCTs involving 303 participants were identified. When comparing  
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59    40    omalizumab to placebo, there was a significant difference in nasal polyps score (mean  
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4 41 difference (MD) = -1.20; 95% confidence interval (CI), -1.48 to -0.92), nasal  
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7 42 congestion score (MD = -0.67; 95% CI, -0.86 to -0.48), Sino-Nasal Outcome Test-22  
8  
9  
10 43 (MD = -15.62; 95% CI, -19.79 to -11.45), total nasal symptom score (MD = -1.84; 95%  
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12  
13 44 CI, -2.43 to -1.25), and reduced need for surgery (risk ratio (RR) = 5.61; 95% CI, 1.99  
14  
15 45 to 15.81). Furthermore, there was no difference in the risk of serious adverse events  
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18 46 ((RR = 1.40; 95% CI, 0.29 to 6.80), adverse events (RR = 0.83; 95% CI, 0.60 to 1.15)  
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20  
21 47 and rescue systemic corticosteroid (RR = 0.52; 95% CI, 0.17 to 1.61).

## 22 23 48 **Conclusions**

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26 49 This was the first meta-analysis that identified omalizumab significantly improved  
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29 50 endoscopic, clinical, and patient-reported outcomes in adults with moderate to severe  
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32 51 CRSwNP and it was safe and well-tolerated.

## 33 34 52 **PROSPERO registration number**

35  
36  
37 53 CRD42020207639.

38  
39  
40 54 **Keywords:** omalizumab; anti-IgE antibody; chronic rhinosinusitis; nasal polyps;  
41  
42 55 systematic review; meta-analysis

## 43 44 56 **Strengths and limitation of this study**

- 45  
46  
47 57 1. This systematic review and meta-analysis was based on a comprehensive search and  
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50 58 included RCTs.  
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53 59 2. Studies were low risk of bias, which was assessed by the Cochrane risk of bias tool.  
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56 60 3. Because the longest follow-up of 4 RCTs was only up to 26 weeks, there were too  
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58  
59 61 short to comprehensively and adequately assess the risks of side effect.

## 62 Introduction

63 Chronic rhinosinusitis (CRS) is common and affects up to 5-12% of the general  
64 population<sup>1</sup>. It is defined as inflammation of the nose and the paranasal sinuses  
65 characterized by nasal congestion, nasal discharge, facial pressure, and loss of smell.  
66 CRS with nasal polyps (CRSwNP) is a severe form of CRS and accounts for 18% of  
67 patients with CRS<sup>2</sup>. CRSwNP is associated with adult-onset asthma, decreased health-  
68 related quality of life (HRQoL)<sup>3, 4</sup>, and substantial economic burden<sup>5</sup>. Many patients  
69 with CRSwNP often fail to achieve sufficient benefit from intranasal corticosteroids  
70 (INCS) or systemic corticosteroids (SCS) and/ or functional endoscopic sinus surgery  
71 (FESS)<sup>6</sup>. Although FESS may be successful initially, relapse occurs in 20% of patients  
72 after 12 months<sup>7</sup>, in 40% after 18 months<sup>8</sup>, and in 80% after 12 years despite ongoing  
73 INCS therapy<sup>9</sup>. Therefore, novel treatments such as biologics are needed for CRSwNP.  
74 Omalizumab (anti-IgE antibody) is one of the biologics and may help patients with  
75 severe CRSwNP. It was reported that omalizumab made their symptom better and  
76 shrank their polyps in small-size randomized controlled trials (RCTs)<sup>10, 11</sup>. But some of  
77 its effectiveness and safety are not well known. Thus, some systematic reviews were  
78 conducted to assess the effectiveness and safety of it. But they found very little  
79 information or insufficient evidence about the use of omalizumab and cannot determine  
80 whether it was effective or not<sup>12, 13</sup>. Currently, some well-designed RCTs about  
81 omalizumab for CRSwNP were published<sup>14</sup>, which may provide us with some evidence.  
82 Therefore, this systematic review was conducted to evaluate the efficacy and safety of

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4 83 omalizumab versus placebo in adult patients with CRSwNP, and identify evidence gaps  
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7 84 that will guide future research on omalizumab for CRSwNP.  
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## 10 85 **Methods**

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13 86 We performed a systematic review based on a priori protocol that was registered with  
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15 87 PROSPERO (No. CRD42020207639)<sup>15</sup>. This review was reported according to the  
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18 88 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)  
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21 89 statement<sup>16</sup> (Additional file 1).  
22

## 23 90 **Eligibility criteria**

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26 91 (a) Population: adult patients (>18) with CRSwNP; (b) Intervention and comparison:  
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29 92 studies comparing omalizumab with placebo, given for at least 16 weeks; (c) Primary  
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32 93 outcomes: nasal polyps score, nasal congestion score, and Sino-Nasal Outcome Test-  
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35 94 22 score; Secondary outcomes: total nasal symptom score, serious adverse events,  
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38 95 adverse events, rescue systemic corticosteroid, and reduced need for surgery. (d)  
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41 96 Study design: randomized controlled trials (RCTs); (e) Studies written and published  
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43  
44 97 in the English language were included.

## 45 98 **Search strategy and selection process**

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48 99 A comprehensive search was performed in PubMed, Embase, Web of Science, and the  
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50  
51 100 Cochrane Library on 13 October 2020. We used the following combined text and  
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54 101 MeSH terms: “nasal polyps”, “sinusitis” and “omalizumab”. Search strategies for major  
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57 102 databases are provided in Appendix 1.  
58  
59 103 Titles and abstracts of the retrieved articles were then screened for their potential  
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4 104 relevance by two reviewers (Q.W Wu and L.X Yuan ). The full-text articles were  
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7 105 obtained and assessed by the same reviewers to determine whether they met the  
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10 106 inclusion criteria for this review. We resolved any differences by a discussion with a  
11  
12 107 third author (Q.T Yang).

### 13 14 15 108 **Data extraction**

16  
17 109 Two reviewers (H.J Qiu and X.Y Wang) read full-text articles and extracted data using  
18  
19  
20 110 a pre-defined extraction form. Data were extracted on the following: first author, year  
21  
22  
23 111 of publication, patient characteristics, study methods, and outcome data.

### 24 25 26 112 **Assessment of risk of bias**

27  
28 113 In this review, the original version of the Cochrane ‘Risk of bias’ tool was used to assess  
29  
30  
31 114 the risk of bias in included studies. The risk of bias was assessed as ‘low’, ‘high’ or  
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33  
34 115 ‘unclear’ for each of the following six domains: sequence generation; allocation  
35  
36  
37 116 concealment; blinding of participants, personnel and outcome assessment; incomplete  
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39  
40 117 outcome data; selective reporting; other sources of bias (if required).

### 41 42 118 **Statistical analysis**

43  
44  
45 119 Study characteristics were shown in tables and described narratively. For dichotomous  
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48 120 data, we planned to analyze treatment differences as a risk ratio (RR) calculated using  
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51 121 the Mantel-Haenszel methods. For continuous outcomes, a generic inverse-variance  
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54 122 method with fixed-effects models was used to calculate pooled mean differences and  
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56  
57 123 95% confidence interval. Statistical heterogeneity was assessed by the Chi<sup>2</sup> test (with a  
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60 124 significance level set at P value < 0.10) and the I<sup>2</sup> statistic (I<sup>2</sup> ≥ 50% indicates

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4 125 substantial heterogeneity). There are two large pharma-sponsored RCTs with most of  
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7 126 the information and two smaller RCTs with effect sizes much larger and much smaller  
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9  
10 127 than the two main studies. A random-effects meta-analysis will exacerbate the effects  
11  
12 128 of the bias. Therefore, we choose a fixed-effect analysis that will be affected less,  
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14  
15 129 although strictly it will also be inappropriate. Sensitivity analysis were performed,  
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17  
18 130 which included the removal of each single study from the meta-analysis one at a time  
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20  
21 131 and recalculation of the summary effect. The possibility of publication bias was  
22  
23 132 assessed by constructing a funnel plot if sufficient studies ( $> 10$ ) were available for an  
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26 133 outcome. All meta-analysis were conducted by the Review Manager (version 5.3).

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4 135 **Results**

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7 136 **Study selection**

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9 137 We identified 1966 studies, of which 3 (with data for 302 participants) were included  
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12 138 in our analysis (Figure 1). The 3 studies (Pinto 2010<sup>10</sup>, Gevaert 2013<sup>11</sup>, and Gavaert  
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14  
15 139 2020<sup>14</sup>) were published between 2010 and 2020, of which Gavaert 2020 reported 2  
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18 140 RCTs (POLYP1 2020 and POLYP2 2020).

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20 141 **Study characteristics**

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23 142 A summary of key participant characteristics, interventions, and comparison pairs was  
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26 143 shown in Table 1. Except for 2 participants in Pinto 2010, all the participants were  
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29 144 adults with CRSwNP. All the studies were double-blind RCTs and used a placebo.  
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31 145 Study duration ranged from 20 weeks to 26 weeks.  
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146 **Table 1.** Summary of characteristics of included RCTs

Study, year	Population	Comorbidity	Omalizumab*	Placebo	Treatment length	Follow-up length	Age (y), mean (Range)		Male, no.(%)	
							Omalizumab	Placebo	Omalizumab	Placebo
Pinto 2010 <sup>10</sup> (n = 14)	CRSwNP (all had undergone endoscopic sinus surgery)	inhaled asthma therapy (72% (5/7) in omalizumab group and 43% (3/7) in placebo group)	subcutaneously	injection, same dose and frequency	26 weeks	26 weeks	43.1 (18-75)	48.6 (18-75)	3 (43%)	7 (100%)
Gevaert <sup>11</sup> 2013 (n = 24)	CRSwNP	asthma (100%)	subcutaneously	injection, same dose and frequency	16 weeks	20 weeks	50 (≥18)	45 (≥18)	12 (80%)	4 (50%)
POLYP1 <sup>14</sup> 2020 (n = 138)	CRSwNP	asthma (58.3% (42/72) in omalizumab group and 48.5% (32/66) in placebo group)	subcutaneously	injection, same dose and frequency	24 weeks	24 weeks	50.0 (18-75)	52.2 (18-75)	47 (65.3)	41 (62.1)
POLYP2 <sup>14</sup> 2020 (n = 127)	CRSwNP	asthma (61.3% (38/62) in omalizumab group and 60% (39/65) in placebo group)	subcutaneously	injection, same dose and frequency	24 weeks	24 weeks	49.0 (18-75)	51.0 (18-75)	39 (62.9)	44 (67.7)

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\*omalizumab subcutaneously (every 2 week or every month injections), based on total serum IgE levels and body weight, with a maximum dose of 375 mg; CRSwNP: chronic rhinosinusitis with nasal polyps; RCTs: randomized controlled trials.



## 149 **Risk of bias and quality of the clinical trials**

150 There were 4 RCTs included in this review. Overall the risk of bias was low, except the  
151 random sequence generation of Pinto 2010 was unclear. Our judgments about each risk  
152 of bias item presented as percentages across all included studies were shown in Figure  
153 2. Our judgments about each risk of bias item for each included study were shown in  
154 Figure 3.

## 155 **Primary outcomes**

156 Total nasal polyps score (NPS) ranges from 0 to 8 (sum of 0-4 for left and right nasal  
157 passage scores per participant), with a lower score indicating smaller-sized nasal polyps  
158 and the highest score indicating large polyps causing complete obstruction of the  
159 inferior nasal cavity.

160 The mean difference (MD) in the change of NPS was -1.20 (95% confidence interval  
161 (CI), -1.48 to -0.92; 4 RCTs; 302 participants;  $I^2 = 90\%$ ; Figure 4A). We noted the high  
162  $I^2$  value and Pinto 2020 had no significant reduction in NPS. However, the removal of  
163 Pinto 2020 did not change the overall effect size in sensitivity analyses. Therefore, we  
164 considered the certainty of the evidence to be high despite the large  $I^2$  value.

165 Nasal congestion score (NCS) was assessed daily by the participant via an electronic  
166 diary as the response to the following question: Is your nose blocked? The four  
167 available response options were scored from 0 (no symptoms) to 3 (severe symptoms).  
168 The pooled mean difference of NCS is -0.67 favoring the groups receiving omalizumab  
169 (95% CI, -0.86 to -0.48; 3 RCTs; 288 participants;  $I^2 = 82\%$ ; Figure 4B). Although the

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4 170 heterogeneity was high in this analysis, all 3 RCTs showed a significant reduction in  
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7 171 NCS with omalizumab.

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9 172 The mean difference in the change of Sino-Nasal Outcome Test-22 (SNOT-22) score  
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12 173 was 15.62 points lower in participants who received omalizumab (MD = -15.62; 95%  
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15 174 CI, -19.79 to -11.45; 265 participants;  $I^2 = 0\%$ ; Figure 4C). There was an improvement  
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18 175 of at least the minimal clinically important difference (MCID;  $\geq 8.9$  points).<sup>17</sup> Because  
19  
20  
21 176 the different measuring tools (Pinto 2010, SNOT-20; Gevaert 2013, Short-Form Health  
22  
23 177 Questionnaire (SF-36)) and unavailable data , these 2 RCTs were excluded in this  
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25  
26 178 pooled analysis.

### 27 28 179 **Secondary outcomes**

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31 180 Total nasal symptom score (TNSS) was defined as the sum of the scores for nasal  
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34 181 congestion score, anterior rhinorrhea score, posterior rhinorrhea score, and sense of  
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37 182 smell score, ranging from 0 (no symptoms) to 12 (most severe symptoms).

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39 183 The mean difference in the change of TNSS was 1.84 points lower in omalizumab  
40  
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42 184 group (MD = -1.84; 95% CI, -2.43 to -1.25; 3 RCTs; 279 participants;  $I^2 = 0\%$ ; Figure  
43  
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45 185 4D).

46  
47 186 No serious adverse events (SAEs) were reported in Gevaert 2013 and Pinto 2010.  
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50 187 However, POLYP1 2020 reported 1 case in the placebo group with myocardial  
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53 188 infarction and POLYP2 2020 reported 1 case of pneumonia in the placebo group and 3  
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56 189 cases in the omalizumab group (1 snake bite, 1 hand fracture, and 1 asthma  
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58 190 exacerbation). The pooled result indicated that there was no difference in the risk of  
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4 191 SAEs (risk ratio (RR) = 1.40; 95% CI, 0.29 to 6.80; 4 RCTs; 302 participants;  $I^2 = 28\%$ ;

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7 192 Figure 5A).

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9 193 There was no difference in the risk of adverse events (AEs) (RR = 0.83; 95% CI, 0.60

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12 194 to 1.15; 4 RCTs; 302 participants;  $I^2 = 0\%$ ; Figure 5B). It was uncertain where or not

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15 195 there was a difference in the risk of rescue systemic corticosteroid (RSCS; RR = 0.52;

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18 196 95% CI, 0.17 to 1.61; 3 RCTs; 279 participants;  $I^2 = 0\%$ ; Figure 5C).

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20 197 Reduced need for surgery (RNS) through week 24 was defined as achievement of NPS

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23 198 of 4 or lower ( $\leq 2$  for each nostril). POLYP1 2020 and POLYP2 2020 reported the

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26 199 number of RNS. The proportion was higher in the group that received omalizumab (RR

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29 200 = 5.61; 95% CI, 1.99 to 15.81; 2 RCTs; 265 participants;  $I^2 = 0\%$ ; Figure 5D).

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## 202 **Discussion**

### 203 **Principal findings**

204 This systematic review and meta-analysis identified 4 RCTs with 302 participants  
205 evaluating the efficacy and safety of omalizumab in CRSwNP. It showed that  
206 omalizumab significantly improved the size of nasal polyps (measured by NPS),  
207 symptoms (measured by NCS and TNSS), and Health-related quality of life (HRQoL;  
208 measured by SNOT-22), and reduce the need for surgery (measured by RNS). What's  
209 more, there was no difference in the risk of SAEs, AEs, and RSCS.

### 210 **Comparison with other studies**

211 Hong included two studies (Gavaert 2013 and Pinto 2010) and made a narrative  
212 systematic review<sup>12</sup>. They concluded that there was insufficient evidence to determine  
213 the effectiveness of omalizumab for CRS. In Chong's systematic review and meta-  
214 analysis, there were 3 small studies with 65 participants (Gavaert 2013, Pinto 2010, and  
215 NCT01066104) evaluated omalizumab<sup>13</sup>. Their results also showed that there were very  
216 uncertain about the effect of omalizumab on disease-specific HRQoL, severe adverse  
217 events, the extent of disease (CT scan scores), generic HRQoL, and adverse effects.  
218 NCT01066104<sup>18</sup> included in Chong's review was unpublished data, so it was excluded  
219 in our study according to our inclusion criteria.

### 220 **Implication for future research and clinical practice**

221 Patients with CRSwNP and comorbid asthma often have a high symptom burden,  
222 substantial impact on HRQoL, a higher risk of RSCS and revision surgery<sup>1</sup>. Moreover,

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4 223 patients with asthma are more likely to develop CRSwNP than are those without asthma,  
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7 224 and they are more likely to receive more oral corticosteroid courses.<sup>19</sup> Therefore, the  
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10 225 risk of RSCS may be due to asthma comorbidity.

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12 226 There were 4 RCTs included in this systematic review, which recruited patients with  
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15 227 moderate to severe CRSwNP. The patients in omalizumab group reduced disease  
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18 228 severity and need for surgery, and experienced significant improvements in HRQoL  
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21 229 (measured by SNOT-22). Placebo-corrected improvements of SNOT-22 was 15.6  
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23  
24 230 points, which exceeded the commonly accepted MCID of 8.9 points.<sup>17,20</sup> Furthermore,  
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26  
27 231 there was no increased risk of SAEs and AEs in patients treated with omalizumab. Thus,  
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30 232 it was certain that omalizumab significantly improved endoscopic, clinical, and patient-  
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33 233 reported outcomes in moderate to severe CRSwNP and it was well tolerated.

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35 234 However, it is still unknown that omalizumab is effective in patients with less severe  
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38 235 CRSwNP (such as serum IgE level <30 IU/mL and NPS=1 for each nostril or unilateral  
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40  
41 236 nostril) and more affordable compared to conventional treatment with topical and  
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43  
44 237 systemic corticosteroids and surgery. Therefore, studies are required to evaluate their  
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47 238 effectiveness in patients with less severe diseases and their cost in the treatment. In  
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50 239 addition, long-term observational studies are also required to determine if omalizumab  
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53 240 lose its effectiveness over time, or whether there are any late adverse events.

#### 54 241 **Limitations of the study**

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56 242 Despite the strict methodology of this systematic review and meta-analysis using  
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59 243 PRISMA guidelines, certain limitations should be considered. First, 4 RCTs were  
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4 244 recruited from the same group with moderate to severe CRSwNP. Therefore, there is  
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7 245 no evidence on whether or not patients with less severe CRSwNP (serum IgE level <30  
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10 246 IU/mL and NPS=1 for each nostril or unilateral nostril) would benefit. Secondly, 4  
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12 247 RCTs were all in adults and no available data for children. Thirdly, because the longest  
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15 248 follow-up of 4 RCTs was only up to 26 weeks, there were too short to comprehensively  
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18 249 and adequately assess the risks of side effect, RSCS, and RNS. Finally, there were only  
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21 250 4 RCTs (<10), so a possibility of publication bias was not assessed by constructing a  
22  
23 251 funnel plot in this systematic review<sup>21</sup>.

## 252 **Conclusions**

253 To the best of our knowledge, this was the first meta-analysis that identified  
254  
255 omalizumab significantly improved endoscopic, clinical, and patient-reported  
256  
257 outcomes in moderate to severe CRSwNP and it was safe and well-tolerated. Studies  
258  
259 are required to evaluate their effectiveness in patients with less severe diseases and their  
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261 cost in the treatment.

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263 N/A.

## 264 **Contributors**

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263 manuscript: Q.W Wu and L.X Yuan. Critical revision of the manuscript for important

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34 274 **Competing interests**

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37 275 No potential conflict of interest was reported by the authors.

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41 276 **Patient consent for publication**

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44 277 Not required.

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48 278 **Patient and public involvement**

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51 279 No patients were involved in the development of the research question, selection of the

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54 280 outcome measures, design and implementation of the study, or interpretation of the

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57 281 results.

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7 283 Not commissioned; externally peer reviewed.  
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11 284 **Data availability statement**  
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14 285 All data relevant to the study are included in the article or uploaded as supplementary  
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17 286 information.  
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355 **Appendix 1.** Search strategies

<b>PubMed</b>
1. nasal polyps[MeSH Terms]
2. (((nasal polyp*[Title/Abstract]) OR (nasal papilloma[Title/Abstract])) OR (nose polyp*[Title/Abstract])) OR (nasi papilloma[Title/Abstract])) OR (nasi polyposis[Title/Abstract])
3. #1 OR #2
4. sinusitis[MeSH Terms]
5. ((((((chronic rhinosinusitis[Title/Abstract]) OR (rhinopolyp*[Title/Abstract])) OR (CRSwNP[Title/Abstract])) OR (sinus Infection*[Title/Abstract])) OR (rhinitis[Title/Abstract])) OR (pansinusitis[Title/Abstract])) OR (sphenoid* sinusitis[Title/Abstract])
6. #4 OR #5
7. omalizumab[MeSH Terms]
8. (((Xolair[Title/Abstract]) OR (anti-IgE antibody[Title/Abstract])) OR (anti-IgE monoclonal antibody[Title/Abstract])) OR (anti-IgE mAb[Title/Abstract])
9. #7 OR #8
10. #3 OR #6
11. #9 AND #10
<b>Cochrane Library</b>
1. MeSH descriptor: [Nasal Polyps] explode all trees
2. (nasal polyp*):ti,ab,kw OR (nasal papilloma):ti,ab,kw OR (nose polyp*):ti,ab,kw OR (nasi papilloma):ti,ab,kw OR (nasi polyposis):ti,ab,kw (Word variations have been searched)
3. #1 OR #2
4. MeSH descriptor: [Sinusitis] explode all trees
5. (chronic rhinosinusitis):ti,ab,kw OR (rhinopolyp*):ti,ab,kw OR (CRSwNP):ti,ab,kw OR (sinus infection*):ti,ab,kw OR (rhinitis):ti,ab,kw (Word variations have been searched)
6. #4 OR #5
7. (pansinusitis):ti,ab,kw OR (sphenoid* sinusitis):ti,ab,kw (Word variations have been searched)
8. #6 OR #7
9. MeSH descriptor: [Omalizumab] explode all trees
10. (Xolair):ti,ab,kw OR (anti-IgE antibody):ti,ab,kw OR (anti-IgE monoclonal antibody):ti,ab,kw OR (anti-IgE mAb):ti,ab,kw (Word variations have been searched)
11. #9 OR #10
12. #3 OR #8
13. #11 AND #12
<b>Embase</b>

1. 'nose polyp'/exp
2. 'nasal polyp\*' OR 'nasal papilloma'/exp OR 'nasal papilloma' OR 'nose polyp\*' OR 'nasi papilloma' OR 'nasi polyposis':ab,ti
3. #1 OR #2
4. 'sinusitis'/exp
5. 'chronic rhinosinusitis rhinopolyp\*' OR crswnp OR 'sinus infection\*' OR rhinitis OR pansinusitis OR 'sphenoid\* sinusitis':ab,ti
6. #4 OR #5
7. #3 OR #6
8. 'omalizumab'/exp
9. 'xolair' OR 'anti-ige antibody' OR 'anti-ige monoclonal antibody' OR 'anti-ige mab':ab,ti
10. #8 OR #9
11. #7 AND #10
12. #7 AND #10 AND [medline]/lim
13. #11 NOT #12

#### Web of Science

1. TOPIC: (nasal polyp\*) OR TOPIC: (nasal papilloma) OR TOPIC: (nose polyp\*) OR TOPIC: (nasi papilloma) OR TOPIC: (nasi polyposis)
2. TOPIC: (sinusitis) OR TOPIC: (chronic rhinosinusitis) OR TOPIC: (rhinopolyp\*) OR TOPIC: (CRSwNP) OR TOPIC: (sinus Infection\*) OR TOPIC: (rhinitis) OR TOPIC: (pansinusitis) OR TOPIC: (sphenoid\* sinusitis)
3. #1 OR #2
4. TOPIC: (omalizumab) OR TOPIC: (Xolair) OR TOPIC: (anti-IgE antibody) OR TOPIC: (anti-IgE monoclonal antibody) OR TOPIC: (anti-IgE mAb)
5. #3 AND #4

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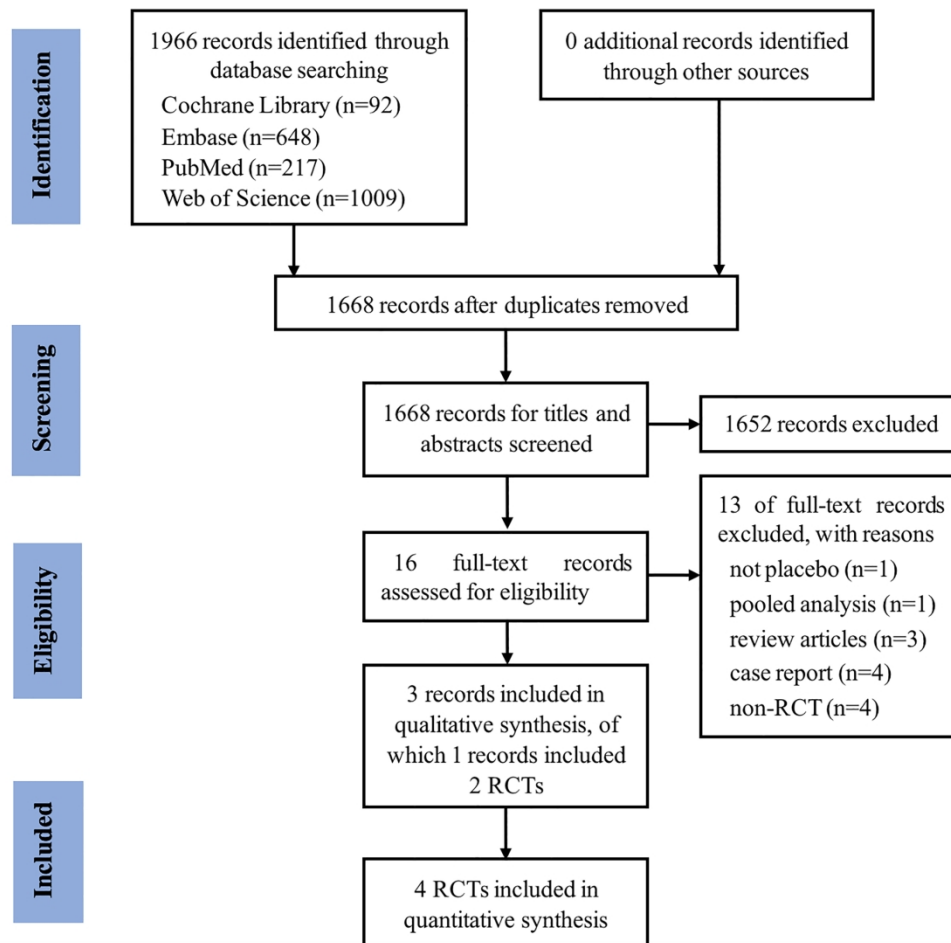
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4 357 **Figure 1.** PRISMA flow diagram of the literature search.  
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7 358 **Figure 2.** ‘Risk of bias’ graph: review authors’ judgements about each risk of bias item  
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9 359 presented as percentages across all included studies.  
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12 360 **Figure 3.** ‘Risk of bias’ summary: review authors’ judgements about each risk of bias  
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14 361 item for each included study.  
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17 362 **Figure 4.** Meta-analyses of omalizumab versus placebo, comparing efficacy and safety.  
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19 363 Outcomes assessed are: (A) Nasal polyps score (NPS), (B) Nasal congestion score  
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21 364 (NCS), (C) Sino-Nasal Outcome Test-22 (SNOT-22), and (D) Total nasal symptom  
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23 365 score (TNSS).  
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28 366 **Figure 5.** Meta-analyses of omalizumab versus placebo, comparing efficacy and safety.  
29  
30 367 Outcomes assessed are: (A) Serious adverse events (SAEs), (B) Adverse events (AEs),  
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32 368 (C) Rescue systemic corticosteroid (RSCS), and (D) Reduced need for surgery (RNS).  
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Figure 1. PRISMA flow diagram of the literature search.

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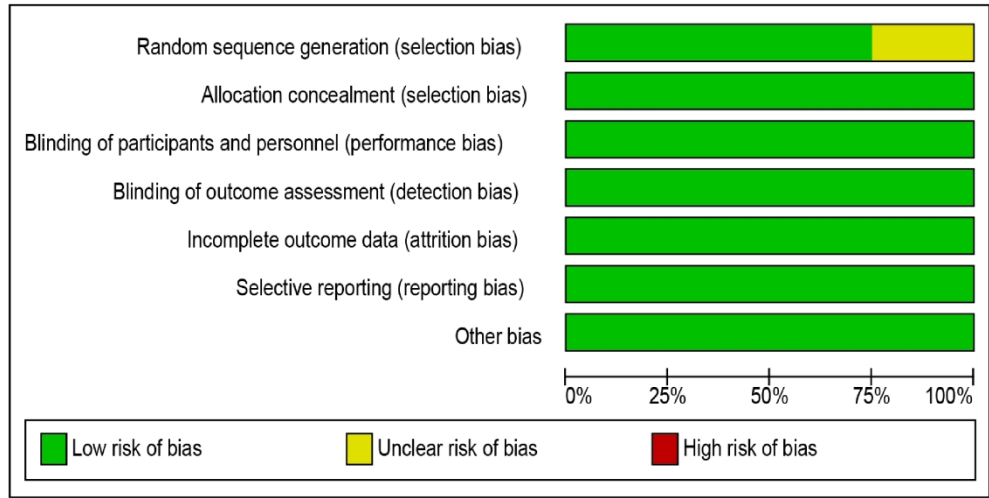


Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gevaert 2013	+	+	+	+	+	+	+
Pinto 2010	?	+	+	+	+	+	+
POLYP1 2020	+	+	+	+	+	+	+
POLYP2 2020	+	+	+	+	+	+	+

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

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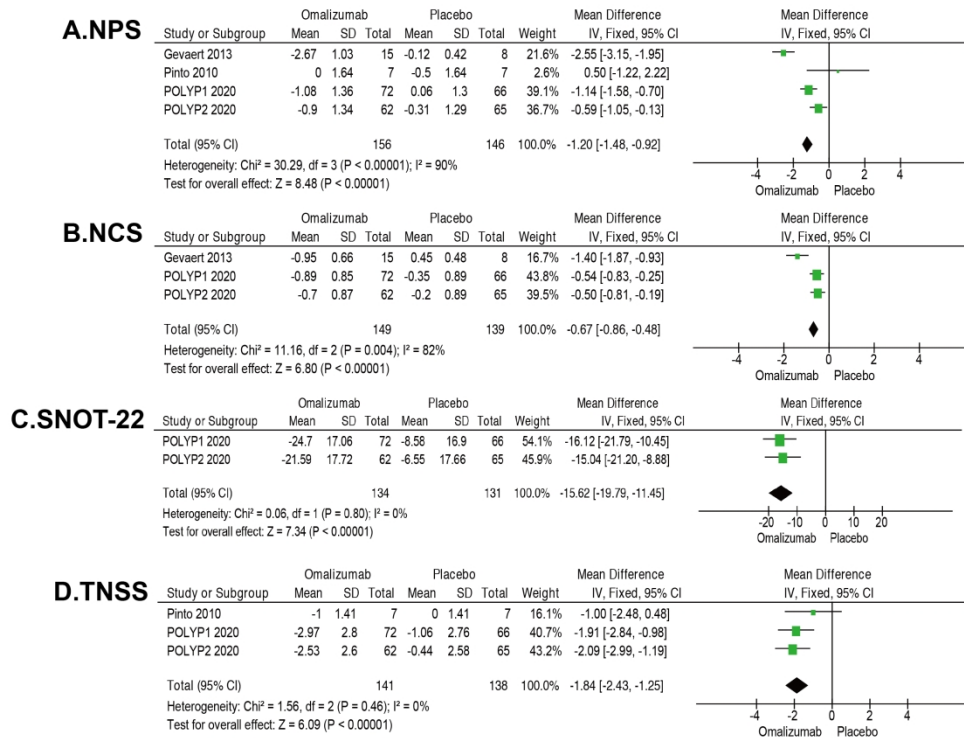


Figure 4. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Nasal polyps score (NPS), (B) Nasal congestion score (NCS), (C) Sino-Nasal Outcome Test-22 (SNOT-22), and (D) Total nasal symptom score (TNSS).

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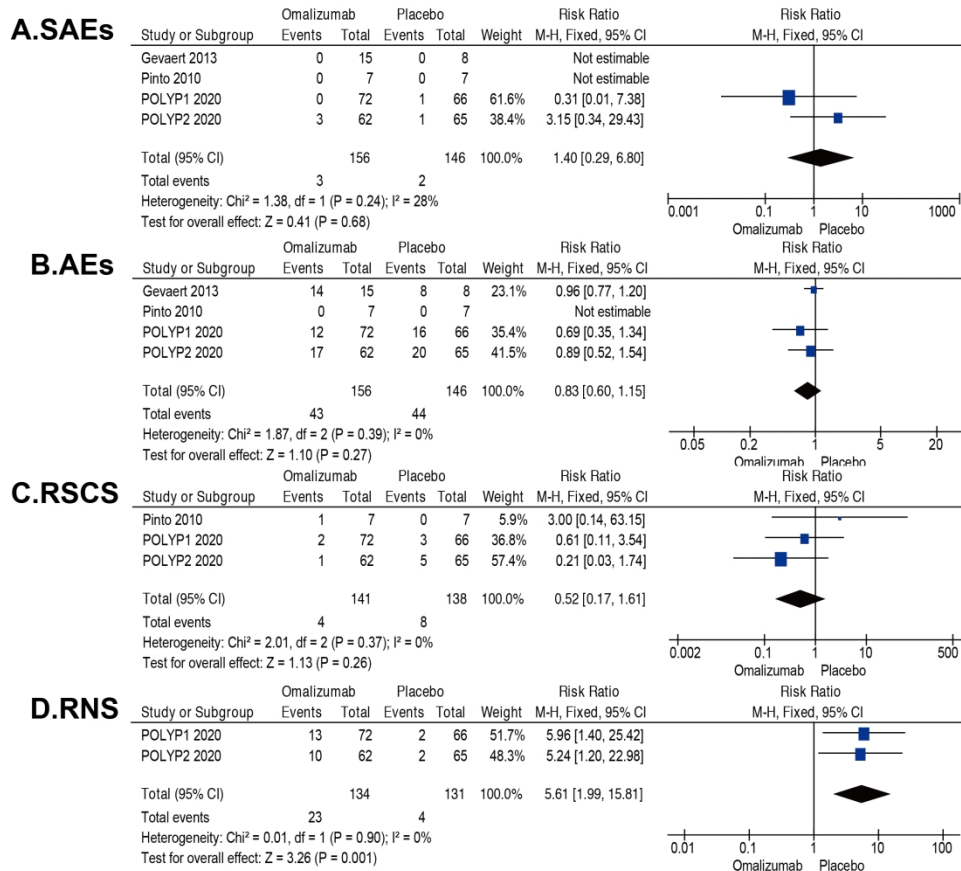


Figure 5. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Serious adverse events (SAEs), (B) Adverse events (AEs), (C) Rescue systemic corticosteroid (RSCS), and (D) Reduced need for surgery (RNS).

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# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	6-7



# PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10; Figure 2 and 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-12; Figure 4 and 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12; Figure 4 and 5.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
<b>FUNDING</b>			



# PRISMA 2009 Checklist

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Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16
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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

Page 2 of 2

For peer review only

# BMJ Open

## Efficacy and safety of omalizumab in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis of randomized controlled trials

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-047344.R2
Article Type:	Original research
Date Submitted by the Author:	28-Jul-2021
Complete List of Authors:	Wu, Qingwu; Third Affiliated Hospital of Sun Yat-Sen University, Department of Otorhinolaryngology-Head and Neck Surgery Yuan, Lianxiong; Third Affiliated Hospital of Sun Yat-Sen University, Department of Science and Research Qiu, Huijun; Third Affiliated Hospital of Sun Yat-Sen University Wang, Xinyue; Third Affiliated Hospital of Sun Yat-Sen University, Otorhinolaryngology-Head and Neck Surgery Huang, Xue-Kun; Third Affiliated Hospital of Sun Yat-Sen University, Department of Otorhinolaryngology-Head and Neck Surgery Zheng, Rui; Third Affiliated Hospital of Sun Yat-Sen University, Department of Otorhinolaryngology-Head and Neck Surgery Yang, Qintai; Third Affiliated Hospital of Sun Yat-Sen University, Department of Otorhinolaryngology-Head and Neck Surgery
<b>Primary Subject Heading</b>:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Ear, nose and throat/otolaryngology
Keywords:	Adult otolaryngology < OTOLARYNGOLOGY, Endoscopic surgery < OTOLARYNGOLOGY, Adverse events < THERAPEUTICS, Clinical trials < THERAPEUTICS

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1 **Efficacy and safety of omalizumab in chronic rhinosinusitis with nasal polyps:**  
2 **a systematic review and meta-analysis of randomized controlled trials**

3 Qingwu Wu<sup>1,2\*</sup>, Lianxiong Yuan<sup>3\*</sup>, Huijun Qiu<sup>1\*</sup>, Xinyue Wang<sup>1</sup>, Xuekun  
4 Huang<sup>1</sup>, Rui Zheng<sup>1,2#</sup>, Qintai Yang<sup>1,2#</sup>

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4     20    **Abstract**

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7     21    **Objectives**

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9     22    To assess the efficacy and safety of omalizumab for chronic rhinosinusitis with nasal  
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12    23    polyps (CRSwNP) and to identify evidence gaps that will guide future research on  
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15    24    omalizumab for CRSwNP.

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17    25    **Design**

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20    26    Systematic review and meta-analysis.

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23    27    **Data Sources**

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26    28    A comprehensive search was performed in PubMed, Embase, Web of Science, and the  
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29    29    Cochrane Library on 13 October 2020.

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31    30    **Eligibility Criteria**

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34    31    Randomized controlled trials (RCTs) comparing omalizumab with placebo, given for  
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37    32    at least 16 weeks in adult patients with CRSwNP.

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39    33    **Data extraction and synthesis**

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42    34    Two independent authors screened search results, extracted data and assessed studies  
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45    35    using the Cochrane risk of bias tool. Data were pooled using the inverse-variance  
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48    36    method and expressed as mean differences (MDs) with 95% CIs. Heterogeneity was  
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51    37    assessed by the Chi<sup>2</sup> test and the I<sup>2</sup> statistic.

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53    38    **Results**

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56    39    A total of 4 RCTs involving 303 participants were identified. When comparing  
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59    40    omalizumab to placebo, there was a significant difference in nasal polyps score (mean  
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4 41 difference (MD) = -1.20; 95% confidence interval (CI), -1.48 to -0.92), nasal  
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7 42 congestion score (MD = -0.67; 95% CI, -0.86 to -0.48), Sino-Nasal Outcome Test-22  
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10 43 (MD = -15.62; 95% CI, -19.79 to -11.45), total nasal symptom score (MD = -1.84; 95%  
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13 44 CI, -2.43 to -1.25), and reduced need for surgery (risk ratio (RR) = 5.61; 95% CI, 1.99  
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15 45 to 15.81). Furthermore, there was no difference in the risk of serious adverse events  
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18 46 ((RR = 1.40; 95% CI, 0.29 to 6.80), adverse events (RR = 0.83; 95% CI, 0.60 to 1.15)  
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21 47 and rescue systemic corticosteroid (RR = 0.52; 95% CI, 0.17 to 1.61).

## 22 23 48 **Conclusions**

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26 49 This was the first meta-analysis that identified omalizumab significantly improved  
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29 50 endoscopic, clinical, and patient-reported outcomes in adults with moderate to severe  
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32 51 CRSwNP and it was safe and well-tolerated.

## 33 34 52 **PROSPERO registration number**

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37 53 CRD42020207639.

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40 54 **Keywords:** omalizumab; anti-IgE antibody; chronic rhinosinusitis; nasal polyps;  
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42 55 systematic review; meta-analysis

## 43 44 56 **Strengths and limitation of this study**

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46  
47 57 1. This systematic review and meta-analysis was based on a comprehensive search and  
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50 58 included RCTs.  
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53 59 2. Studies were low risk of bias, which was assessed by the Cochrane risk of bias tool.  
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56 60 3. Because the longest follow-up of 4 RCTs was only up to 26 weeks, there were too  
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59 61 short to comprehensively and adequately assess the risks of side effect.

## 62 Introduction

63 Chronic rhinosinusitis (CRS) is common and affects up to 5-12% of the general  
64 population<sup>1</sup>. It is defined as inflammation of the nose and the paranasal sinuses  
65 characterized by nasal congestion, nasal discharge, facial pressure, and loss of smell.  
66 CRS with nasal polyps (CRSwNP) is a severe form of CRS and accounts for 18% of  
67 patients with CRS<sup>2</sup>. CRSwNP is associated with adult-onset asthma, decreased health-  
68 related quality of life (HRQoL)<sup>3, 4</sup>, and substantial economic burden<sup>5</sup>. Many patients  
69 with CRSwNP often fail to achieve sufficient benefit from intranasal corticosteroids  
70 (INCS) or systemic corticosteroids (SCS) and/ or functional endoscopic sinus surgery  
71 (FESS)<sup>6</sup>. Although FESS may be successful initially, relapse occurs in 20% of patients  
72 after 12 months<sup>7</sup>, in 40% after 18 months<sup>8</sup>, and in 80% after 12 years despite ongoing  
73 INCS therapy<sup>9</sup>. Therefore, novel treatments such as biologics are needed for CRSwNP.  
74 Omalizumab (anti-IgE antibody) is one of the biologics and may help patients with  
75 severe CRSwNP. It was reported that omalizumab made their symptom better and  
76 shrank their polyps in small-size randomized controlled trials (RCTs)<sup>10, 11</sup>. But some of  
77 its effectiveness and safety are not well known. Thus, some systematic reviews were  
78 conducted to assess the effectiveness and safety of it. But they found very little  
79 information or insufficient evidence about the use of omalizumab and cannot determine  
80 whether it was effective or not<sup>12, 13</sup>. Currently, some well-designed RCTs about  
81 omalizumab for CRSwNP were published<sup>14</sup>, which may provide us with some evidence.  
82 Therefore, this systematic review was conducted to evaluate the efficacy and safety of

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4 83 omalizumab versus placebo in adult patients with CRSwNP, and identify evidence gaps  
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7 84 that will guide future research on omalizumab for CRSwNP.  
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## 10 **Methods**

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13 86 We performed a systematic review based on a priori protocol that was registered with  
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15 87 PROSPERO (No. CRD42020207639)<sup>15</sup>. This review was reported according to the  
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18 88 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)  
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20  
21 89 statement<sup>16</sup> (Additional file 1).  
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## 24 **Eligibility criteria**

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26 91 (a) Population: adult patients (>18) with CRSwNP; (b) Intervention and comparison:  
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29 92 studies comparing omalizumab with placebo, given for at least 16 weeks; (c) Primary  
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32 93 outcomes: nasal polyps score, nasal congestion score, and Sino-Nasal Outcome Test-  
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35 94 22 score; Secondary outcomes: total nasal symptom score, serious adverse events,  
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38 95 adverse events, rescue systemic corticosteroid, and reduced need for surgery. (d)  
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40 96 Study design: randomized controlled trials (RCTs); (e) Studies written and published  
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43 97 in the English language were included.  
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## 45 **Search strategy and selection process**

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48 99 A comprehensive search was performed in PubMed, Embase, Web of Science, and the  
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51 100 Cochrane Library on 13 October 2020. We used the following combined text and  
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54 101 MeSH terms: “nasal polyps”, “sinusitis” and “omalizumab”. Search strategies for major  
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57 102 databases are provided in Appendix 1.  
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59 103 Titles and abstracts of the retrieved articles were then screened for their potential  
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4 104 relevance by two reviewers (Q.W Wu and L.X Yuan ). The full-text articles were  
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7 105 obtained and assessed by the same reviewers to determine whether they met the  
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10 106 inclusion criteria for this review. We resolved any differences by a discussion with a  
11  
12 107 third author (Q.T Yang).

### 15 108 **Data extraction**

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17 109 Two reviewers (H.J Qiu and X.Y Wang) read full-text articles and extracted data using  
18  
19  
20 110 a pre-defined extraction form. Data were extracted on the following: first author, year  
21  
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23 111 of publication, patient characteristics, study methods, and outcome data.

### 25 112 **Assessment of risk of bias**

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28 113 In this review, the original version of the Cochrane 'Risk of bias' tool was used to assess  
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30  
31 114 the risk of bias in included studies. The risk of bias was assessed as 'low', 'high' or  
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34 115 'unclear' for each of the following six domains: sequence generation; allocation  
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37 116 concealment; blinding of participants, personnel and outcome assessment; incomplete  
38  
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40 117 outcome data; selective reporting; other sources of bias (if required).

### 42 118 **Statistical analysis**

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45 119 Study characteristics were shown in tables and described narratively. For dichotomous  
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48 120 data, we planned to analyze treatment differences as a risk ratio (RR) calculated using  
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51 121 the Mantel-Haenszel methods. For continuous outcomes, a generic inverse-variance  
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54 122 method with fixed-effects models was used to calculate pooled mean differences and  
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56  
57 123 95% confidence interval. Statistical heterogeneity was assessed by the Chi<sup>2</sup> test (with a  
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60 124 significance level set at P value <0.10) and the I<sup>2</sup> statistic (I<sup>2</sup> ≥ 50% indicates

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4 125 substantial heterogeneity). There are two large pharma-sponsored RCTs with most of  
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7 126 the information and two smaller RCTs with effect sizes much larger and much smaller  
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10 127 than the two main studies. A random-effects meta-analysis may exacerbate the effects  
11  
12 128 of the bias and a fixed-effect analysis will be affected less, although strictly fixed-effect  
13  
14  
15 129 analysis will also be inappropriate.<sup>17</sup> Therefore, we choose a fixed-effect analysis in  
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17  
18 130 this study. Sensitivity analysis were performed, which included the removal of each  
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20  
21 131 single study from the meta-analysis one at a time and recalculation of the summary  
22  
23 132 effect. The possibility of publication bias was assessed by constructing a funnel plot if  
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26 133 sufficient studies (>10) were available for an outcome. All meta-analysis were  
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29 134 conducted by the Review Manager (version 5.3).

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4 136 **Results**

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7 137 **Study selection**

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9 138 We identified 1966 studies, of which 3 (with data for 302 participants) were included  
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12 139 in our analysis (Figure 1). The 3 studies (Pinto 2010<sup>10</sup>, Gevaert 2013<sup>11</sup>, and Gavaert  
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15 140 2020<sup>14</sup>) were published between 2010 and 2020, of which Gavaert 2020 reported 2  
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18 141 RCTs (POLYP1 2020 and POLYP2 2020).

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20 142 **Study characteristics**

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23 143 A summary of key participant characteristics, interventions, and comparison pairs was  
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26 144 shown in Table 1. Except for 2 participants in Pinto 2010, all the participants were  
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29 145 adults with CRSwNP. All the studies were double-blind RCTs and used a placebo.  
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31 146 Study duration ranged from 20 weeks to 26 weeks.  
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147 **Table 1.** Summary of characteristics of included RCTs

Study, year	Population	Comorbidity	Omalizumab*	Placebo	Treatment length	Follow-up length	Age (y), mean (Range)		Male, no.(%)	
							Omalizumab	Placebo	Omalizumab	Placebo
Pinto 2010 <sup>10</sup> (n = 14)	CRSwNP (all had undergone endoscopic sinus surgery)	inhaled asthma therapy (72% (5/7) in omalizumab group and 43% (3/7) in placebo group)	subcutaneously	injection, same dose and frequency	26 weeks	26 weeks	43.1 (18-75)	48.6 (18-75)	3 (43%)	7 (100%)
Gevaert <sup>11</sup> 2013 (n = 24)	CRSwNP	asthma (100%)	subcutaneously	injection, same dose and frequency	16 weeks	20 weeks	50 (≥18)	45 (≥18)	12 (80%)	4 (50%)
POLYP1 <sup>14</sup> 2020 (n = 138)	CRSwNP	asthma (58.3% (42/72) in omalizumab group and 48.5% (32/66) in placebo group)	subcutaneously	injection, same dose and frequency	24 weeks	24 weeks	50.0 (18-75)	52.2 (18-75)	47 (65.3)	41 (62.1)
POLYP2 <sup>14</sup> 2020 (n = 127)	CRSwNP	asthma (61.3% (38/62) in omalizumab group and 60% (39/65) in placebo group)	subcutaneously	injection, same dose and frequency	24 weeks	24 weeks	49.0 (18-75)	51.0 (18-75)	39 (62.9)	44 (67.7)

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\*omalizumab subcutaneously (every 2 week or every month injections), based on total serum IgE levels and body weight, with a maximum dose of 375 mg; CRSwNP: chronic rhinosinusitis with nasal polyps; RCTs: randomized controlled trials.



## 150 **Risk of bias and quality of the clinical trials**

151 There were 4 RCTs included in this review. Overall the risk of bias was low, except the  
152 random sequence generation of Pinto 2010 was unclear. Our judgments about each risk  
153 of bias item presented as percentages across all included studies were shown in Figure  
154 2. Our judgments about each risk of bias item for each included study were shown in  
155 Figure 3.

## 156 **Primary outcomes**

157 Total nasal polyps score (NPS) ranges from 0 to 8 (sum of 0-4 for left and right nasal  
158 passage scores per participant), with a lower score indicating smaller-sized nasal polyps  
159 and the highest score indicating large polyps causing complete obstruction of the  
160 inferior nasal cavity.

161 The mean difference (MD) in the change of NPS was -1.20 (95% confidence interval  
162 (CI), -1.48 to -0.92; 4 RCTs; 302 participants;  $I^2 = 90\%$ ; Figure 4A). We noted the high  
163  $I^2$  value and Pinto 2020 had no significant reduction in NPS. However, the removal of  
164 Pinto 2020 did not change the overall effect size in sensitivity analyses. Therefore, we  
165 considered the certainty of the evidence to be high despite the large  $I^2$  value.

166 Nasal congestion score (NCS) was assessed daily by the participant via an electronic  
167 diary as the response to the following question: Is your nose blocked? The four  
168 available response options were scored from 0 (no symptoms) to 3 (severe symptoms).  
169 The pooled mean difference of NCS is -0.67 favoring the groups receiving omalizumab  
170 (95% CI, -0.86 to -0.48; 3 RCTs; 288 participants;  $I^2 = 82\%$ ; Figure 4B). Although the

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4 171 heterogeneity was high in this analysis, all 3 RCTs showed a significant reduction in  
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7 172 NCS with omalizumab.

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9 173 The mean difference in the change of Sino-Nasal Outcome Test-22 (SNOT-22) score  
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12 174 was 15.62 points lower in participants who received omalizumab (MD = -15.62; 95%  
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15 175 CI, -19.79 to -11.45; 265 participants;  $I^2 = 0\%$ ; Figure 4C). There was an improvement  
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18 176 of at least the minimal clinically important difference (MCID;  $\geq 8.9$  points).<sup>18</sup> Because  
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20  
21 177 the different measuring tools (Pinto 2010, SNOT-20; Gevaert 2013, Short-Form Health  
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23 178 Questionnaire (SF-36)) and unavailable data , these 2 RCTs were excluded in this  
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25  
26 179 pooled analysis.

## 27 28 180 **Secondary outcomes**

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31 181 Total nasal symptom score (TNSS) was defined as the sum of the scores for nasal  
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34 182 congestion score, anterior rhinorrhea score, posterior rhinorrhea score, and sense of  
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37 183 smell score, ranging from 0 (no symptoms) to 12 (most severe symptoms).

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39 184 The mean difference in the change of TNSS was 1.84 points lower in omalizumab  
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42 185 group (MD = -1.84; 95% CI, -2.43 to -1.25; 3 RCTs; 279 participants;  $I^2 = 0\%$ ; Figure  
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45 186 4D).

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47 187 No serious adverse events (SAEs) were reported in Gevaert 2013 and Pinto 2010.  
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49  
50 188 However, POLYP1 2020 reported 1 case in the placebo group with myocardial  
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53 189 infarction and POLYP2 2020 reported 1 case of pneumonia in the placebo group and 3  
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56 190 cases in the omalizumab group (1 snake bite, 1 hand fracture, and 1 asthma  
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58 191 exacerbation). The pooled result indicated that there was no difference in the risk of  
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4 192 SAEs (risk ratio (RR) = 1.40; 95% CI, 0.29 to 6.80; 4 RCTs; 302 participants;  $I^2 = 28\%$ ;

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7 193 Figure 5A).

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9 194 There was no difference in the risk of adverse events (AEs) (RR = 0.83; 95% CI, 0.60

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12 195 to 1.15; 4 RCTs; 302 participants;  $I^2 = 0\%$ ; Figure 5B). It was uncertain where or not

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15 196 there was a difference in the risk of rescue systemic corticosteroid (RSCS; RR = 0.52;

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18 197 95% CI, 0.17 to 1.61; 3 RCTs; 279 participants;  $I^2 = 0\%$ ; Figure 5C).

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20 198 Reduced need for surgery (RNS) through week 24 was defined as achievement of NPS

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23 199 of 4 or lower ( $\leq 2$  for each nostril). POLYP1 2020 and POLYP2 2020 reported the

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26 200 number of RNS. The proportion was higher in the group that received omalizumab (RR

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29 201 = 5.61; 95% CI, 1.99 to 15.81; 2 RCTs; 265 participants;  $I^2 = 0\%$ ; Figure 5D).

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## 203 **Discussion**

### 204 **Principal findings**

205 This systematic review and meta-analysis identified 4 RCTs with 302 participants  
206 evaluating the efficacy and safety of omalizumab in CRSwNP. It showed that  
207 omalizumab significantly improved the size of nasal polyps (measured by NPS),  
208 symptoms (measured by NCS and TNSS), and Health-related quality of life (HRQoL;  
209 measured by SNOT-22), and reduce the need for surgery (measured by RNS). What's  
210 more, there was no difference in the risk of SAEs, AEs, and RSCS.

### 211 **Comparison with other studies**

212 Hong included two studies (Gavaert 2013 and Pinto 2010) and made a narrative  
213 systematic review<sup>12</sup>. They concluded that there was insufficient evidence to determine  
214 the effectiveness of omalizumab for CRS. In Chong's systematic review and meta-  
215 analysis, there were 3 small studies with 65 participants (Gavaert 2013, Pinto 2010, and  
216 NCT01066104) evaluated omalizumab<sup>13</sup>. Their results also showed that there were very  
217 uncertain about the effect of omalizumab on disease-specific HRQoL, severe adverse  
218 events, the extent of disease (CT scan scores), generic HRQoL, and adverse effects.  
219 NCT01066104<sup>19</sup> included in Chong's review was unpublished data, so it was excluded  
220 in our study according to our inclusion criteria.

### 221 **Implication for future research and clinical practice**

222 Patients with CRSwNP and comorbid asthma often have a high symptom burden,  
223 substantial impact on HRQoL, a higher risk of RSCS and revision surgery<sup>1</sup>. Moreover,

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4 224 patients with asthma are more likely to develop CRSwNP than are those without asthma,  
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7 225 and they are more likely to receive more oral corticosteroid courses.<sup>20</sup> Therefore, the  
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10 226 risk of RSCS may be due to asthma comorbidity.

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12 227 There were 4 RCTs included in this systematic review, which recruited patients with  
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15 228 moderate to severe CRSwNP. The patients in omalizumab group reduced disease  
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18 229 severity and need for surgery, and experienced significant improvements in HRQoL  
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21 230 (measured by SNOT-22). Placebo-corrected improvements of SNOT-22 was 15.6  
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23  
24 231 points, which exceeded the commonly accepted MCID of 8.9 points.<sup>18, 21</sup> Furthermore,  
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26  
27 232 there was no increased risk of SAEs and AEs in patients treated with omalizumab. Thus,  
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30 233 it was certain that omalizumab significantly improved endoscopic, clinical, and patient-  
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33 234 reported outcomes in moderate to severe CRSwNP and it was well tolerated.

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35 235 However, it is still unknown that omalizumab is effective in patients with less severe  
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37 236 CRSwNP (such as NPS=1 for each nostril or unilateral nostril) and more affordable  
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40 237 compared to conventional treatment with topical and systemic corticosteroids and  
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43 238 surgery. Therefore, studies are required to evaluate their effectiveness in patients with  
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46 239 less severe diseases and their cost in the treatment. In addition, long-term observational  
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49 240 studies are also required to determine if omalizumab lose its effectiveness over time, or  
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51  
52 241 whether there are any late adverse events.

### 53 242 **Limitations of the study**

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55 243 Despite the strict methodology of this systematic review and meta-analysis using  
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58 244 PRISMA guidelines, certain limitations should be considered. First, 4 RCTs were  
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4 245 recruited from the same group with moderate to severe CRSwNP. Therefore, there is  
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7 246 no evidence on whether or not patients with less severe CRSwNP (NPS=1 for each  
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10 247 nostril or unilateral nostril) would benefit. Secondly, 4 RCTs were all in adults and no  
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12 248 available data for children. Thirdly, because the longest follow-up of 4 RCTs was only  
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15 249 up to 26 weeks, there were too short to comprehensively and adequately assess the risks  
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18 250 of side effect, RSCS, and RNS. Finally, there were only 4 RCTs (<10), so a possibility  
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21 251 of publication bias was not assessed by constructing a funnel plot in this systematic  
22  
23 252 review<sup>17</sup>.

### 253 **Conclusions**

254 To the best of our knowledge, this was the first meta-analysis that identified  
255 omalizumab significantly improved endoscopic, clinical, and patient-reported  
256 outcomes in moderate to severe CRSwNP and it was safe and well-tolerated. Studies  
257 are required to evaluate their effectiveness in patients with less severe diseases and their  
258 cost in the treatment.

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### 261 **Contributors**

262 Concept and design: R Zheng and Q.T Yang. Acquisition, analysis, or interpretation of  
263 data: Q.W Wu, L.X Yuan, H.J Qiu, X.Y Wang, and X.K Huang. Drafting of the  
264 manuscript: Q.W Wu and L.X Yuan. Critical revision of the manuscript for important

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7 266 R Zheng and Q.T Yang.  
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33 275 **Competing interests**  
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37 276 No potential conflict of interest was reported by the authors.  
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40 277 **Patient consent for publication**  
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44 278 Not required.  
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47 279 **Patient and public involvement**  
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51 280 No patients were involved in the development of the research question, selection of the  
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54 281 outcome measures, design and implementation of the study, or interpretation of the  
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57 282 results.  
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4 283 **Provenance and peer review**

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7 284 Not commissioned; externally peer reviewed.  
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11 285 **Data availability statement**

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14 286 All data relevant to the study are included in the article or uploaded as supplementary  
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17 287 information.  
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30  
31 291 **Ethics approval**

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34 292 It was not required.  
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25 353 *rhinology* 2018; 8: 495-503. DOI: 10.1002/alr.22064.  
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27 354 21. Hopkins C, Gillett S, Slack R, et al. Psychometric validity of the 22-item Sinonasal  
28 355 Outcome Test. *Clin Otolaryngol* 2009; 34: 447-454. DOI: 10.1111/j.1749-  
29 356 4486.2009.01995.x.  
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4 358 **Figure 1.** PRISMA flow diagram of the literature search.

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7 359 **Figure 2.** ‘Risk of bias’ graph: review authors’ judgements about each risk of bias item  
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9 360 presented as percentages across all included studies.

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12 361 **Figure 3.** ‘Risk of bias’ summary: review authors’ judgements about each risk of bias  
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15 362 item for each included study.

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17 363 **Figure 4.** Meta-analyses of omalizumab versus placebo, comparing efficacy and safety.  
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20 364 Outcomes assessed are: (A) Nasal polyps score (NPS), (B) Nasal congestion score  
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23 365 (NCS), (C) Sino-Nasal Outcome Test-22 (SNOT-22), and (D) Total nasal symptom  
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26 366 score (TNSS).

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28 367 **Figure 5.** Meta-analyses of omalizumab versus placebo, comparing efficacy and safety.  
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31 368 Outcomes assessed are: (A) Serious adverse events (SAEs), (B) Adverse events (AEs),  
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34 369 (C) Rescue systemic corticosteroid (RSCS), and (D) Reduced need for surgery (RNS).  
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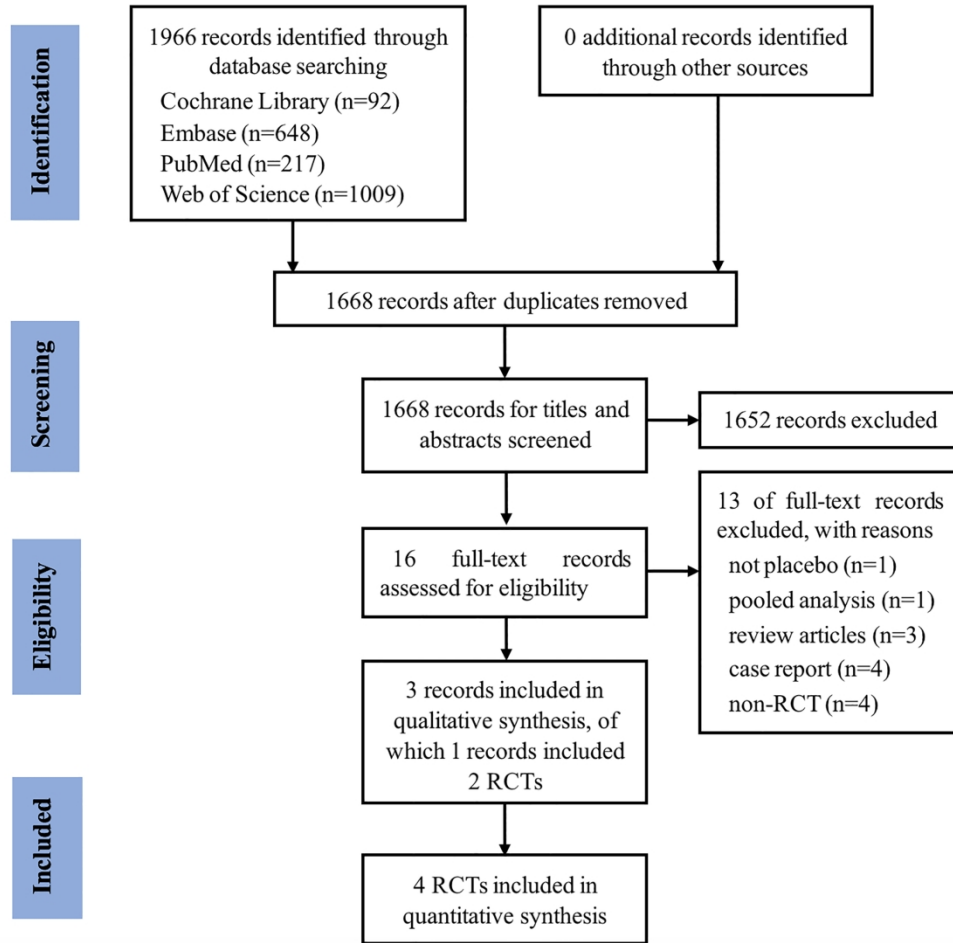


Figure 1. PRISMA flow diagram of the literature search.

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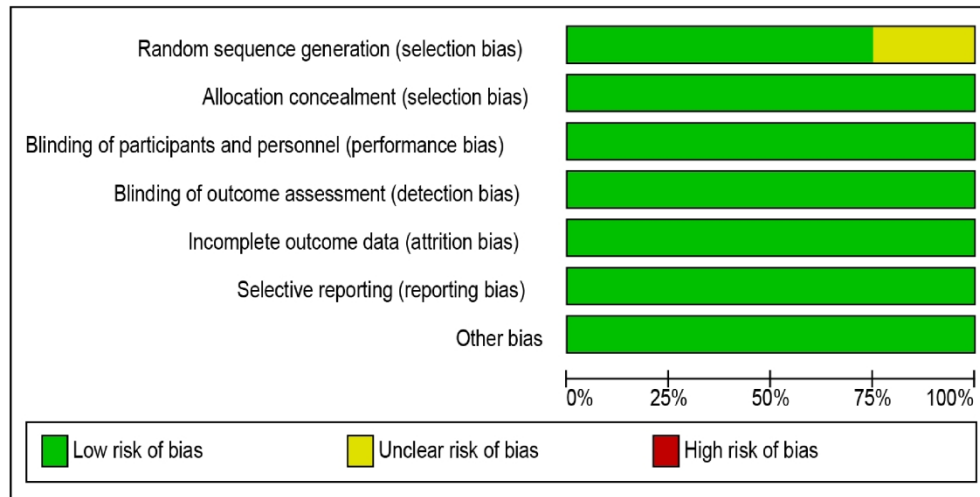


Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gevaert 2013	+	+	+	+	+	+	+
Pinto 2010	?	+	+	+	+	+	+
POLYP1 2020	+	+	+	+	+	+	+
POLYP2 2020	+	+	+	+	+	+	+

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

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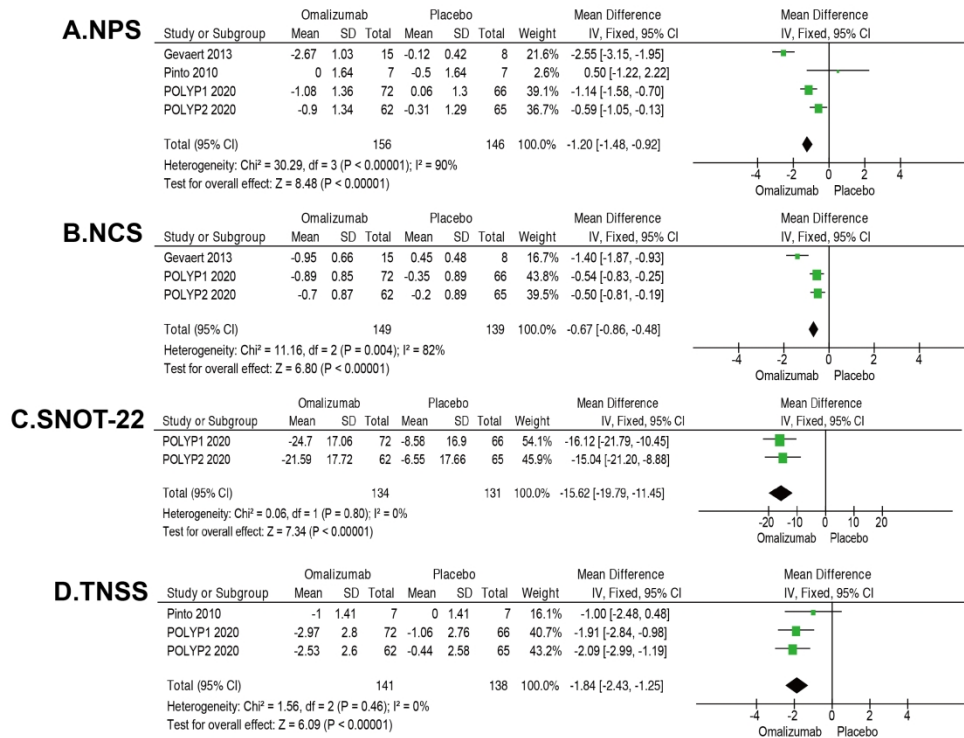


Figure 4. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Nasal polyps score (NPS), (B) Nasal congestion score (NCS), (C) Sino-Nasal Outcome Test-22 (SNOT-22), and (D) Total nasal symptom score (TNSS).

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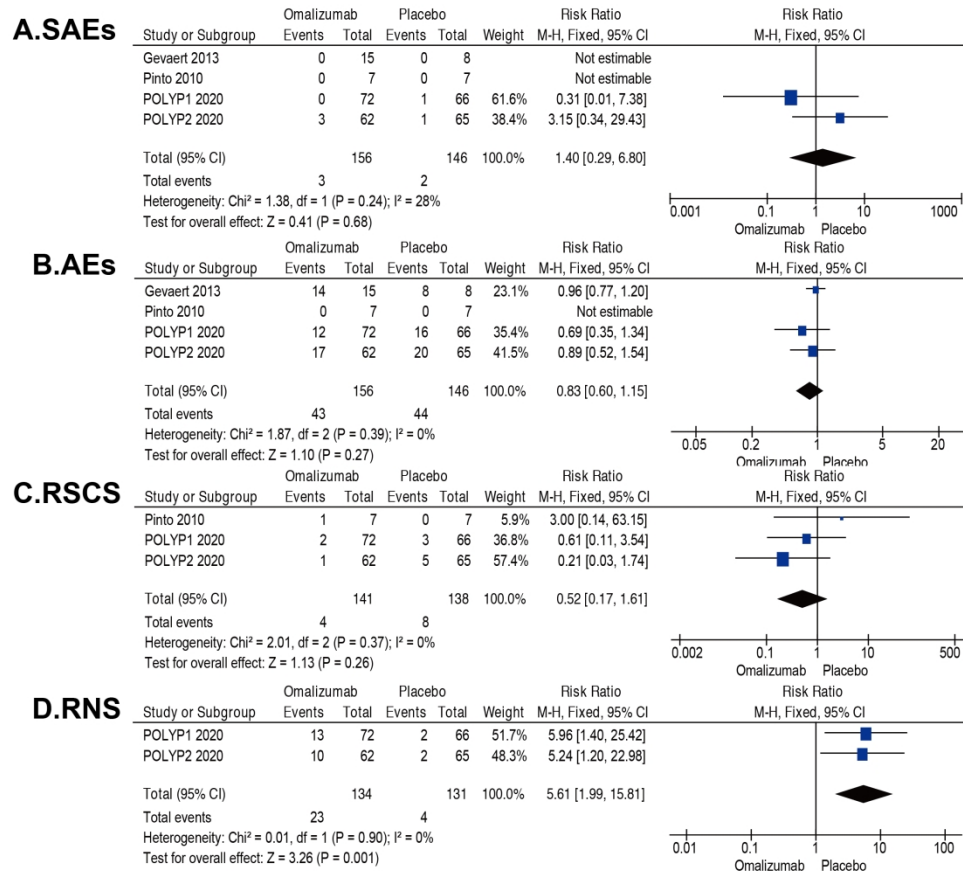


Figure 5. Meta-analyses of omalizumab versus placebo, comparing efficacy and safety. Outcomes assessed are: (A) Serious adverse events (SAEs), (B) Adverse events (AEs), (C) Rescue systemic corticosteroid (RSCS), and (D) Reduced need for surgery (RNS).

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**Appendix. Search strategies**

<b>PubMed</b>
1. nasal polyps[MeSH Terms]
2. (((nasal polyp*[Title/Abstract]) OR (nasal papilloma[Title/Abstract])) OR (nose polyp*[Title/Abstract])) OR (nasi papilloma[Title/Abstract]) OR (nasi polyposis[Title/Abstract])
3. #1 OR #2
4. sinusitis[MeSH Terms]
5. ((((((chronic rhinosinusitis[Title/Abstract]) OR (rhinopolyp*[Title/Abstract])) OR (CRSwNP[Title/Abstract])) OR (sinus Infection*[Title/Abstract])) OR (rhinitis[Title/Abstract])) OR (pansinusitis[Title/Abstract]) OR (sphenoid* sinusitis[Title/Abstract]))
6. #4 OR #5
7. omalizumab[MeSH Terms]
8. (((Xolair[Title/Abstract]) OR (anti-IgE antibody[Title/Abstract])) OR (anti-IgE monoclonal antibody[Title/Abstract])) OR (anti-IgE mAb[Title/Abstract])
9. #7 OR #8
10. #3 OR #6
11. #9 AND #10
<b>Cochrane Library</b>
1. MeSH descriptor: [Nasal Polyps] explode all trees
2. (nasal polyp*):ti,ab,kw OR (nasal papilloma):ti,ab,kw OR (nose polyp*):ti,ab,kw OR (nasi papilloma):ti,ab,kw OR (nasi polyposis):ti,ab,kw (Word variations have been searched)
3. #1 OR #2
4. MeSH descriptor: [Sinusitis] explode all trees
5. (chronic rhinosinusitis):ti,ab,kw OR (rhinopolyp*):ti,ab,kw OR (CRSwNP):ti,ab,kw OR (sinus infection*):ti,ab,kw OR (rhinitis):ti,ab,kw (Word variations have been searched)
6. #4 OR #5
7. (pansinusitis):ti,ab,kw OR (sphenoid* sinusitis):ti,ab,kw (Word variations have been searched)
8. #6 OR #7
9. MeSH descriptor: [Omalizumab] explode all trees
10. (Xolair):ti,ab,kw OR (anti-IgE antibody):ti,ab,kw OR (anti-IgE monoclonal antibody):ti,ab,kw OR (anti-IgE mAb):ti,ab,kw (Word variations have been searched)
11. #9 OR #10
12. #3 OR #8
13. #11 AND #12
<b>Embase</b>
1. 'nose polyp'/exp
2. 'nasal polyp*' OR 'nasal papilloma'/exp OR 'nasal papilloma' OR 'nose polyp*' OR

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3 'nasi papilloma' OR 'nasi polyposis':ab,ti  
4 3. #1 OR #2  
5 4. 'sinusitis'/exp  
6 5. 'chronic rhinosinusitis rhinopolyp\*' OR crswnp OR 'sinus infection\*' OR rhinitis  
7 OR pansinusitis OR 'sphenoid\* sinusitis':ab,ti  
8 6. #4 OR #5  
9 7. #3 OR #6  
10 8. 'omalizumab'/exp  
11 9. 'xolair' OR 'anti-ige antibody' OR 'anti-ige monoclonal antibody' OR 'anti-ige  
12 mab':ab,ti  
13 10. #8 OR #9  
14 11. #7 AND #10  
15 12. #7 AND #10 AND [medline]/lim  
16 13. #11 NOT #12  
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### Web of Science

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23 1. TOPIC: (nasal polyp\*) OR TOPIC: (nasal papilloma) OR TOPIC: (nose polyp\*)  
24 OR TOPIC: (nasi papilloma) OR TOPIC: (nasi polyposis)  
25 2. TOPIC: (sinusitis) OR TOPIC: (chronic rhinosinusitis) OR TOPIC: (rhinopolyp\*)  
26 OR TOPIC: (CRSwNP) OR TOPIC: (sinus Infection\*) OR TOPIC: (rhinitis) OR  
27 TOPIC: (pansinusitis) OR TOPIC: (sphenoid\* sinusitis)  
28 3. #1 OR #2  
29 4. TOPIC: (omalizumab) OR TOPIC: (Xolair) OR TOPIC: (anti-IgE antibody) OR  
30 TOPIC: (anti-IgE monoclonal antibody) OR TOPIC: (anti-IgE mAb)  
31 5. #3 AND #4  
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# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	6-7



# PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10; Figure 2 and 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-12; Figure 4 and 5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12; Figure 4 and 5.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
<b>FUNDING</b>			



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Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16
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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

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For peer review only