PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and safety of omalizumab in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis of randomized controlled trials
AUTHORS	Wu, Qingwu; Yuan, Lianxiong; Qiu, Huijun; Wang, Xinyue; Huang, Xue-Kun; Zheng, Rui; Yang, Qintai

VERSION 1 – REVIEW

REVIEWER	Novosad, Jakub University Hospital Hradec Kralove, Institute of clinical immunology and allergy
REVIEW RETURNED	15-Dec-2020

GENERAL COMMENTS	Dear authors, I have read with particular interest your submitted article covering the very actual issue, a biological therapy of CRSwNP. I found it very understandably and clearly written with logic structure. All used statistical methods are relevant and explained with clarity. I found only some typos (page 12, line 15, PRIMSA). Thank you for a very interesting work!

REVIEWER	Konstantinou, George 424 General Military Training Hospital, Allergy and Clinical Immunology
REVIEW RETURNED	24-Dec-2020

GENERAL COMMENTS	The submitted article is an interesting and well-conducted systematic review and meta-analysis. My comments: In the Methods section: 1. Add the “Minimally Clinically Important Difference” (MCID) for each of the outcomes of interest that were meta-analyzed. This will help the average reader to better appreciate not only the statistical but also the clinical importance of the calculated changes presented in the results. 2. Describe in a couple of sentences how the nasal polyp score was calculated, which parameters were assessed in the other outcomes of interest (nasal congestion score and total nasal symptom score), and how the need for surgery was defined.

	3. Was the nasal congestion score based on PROs or VAS in each of the studies included in the meta-analysis? In the “Primary Outcomes” section: 4. Provide the mean change for SNOT-22. 5. In the results, explain whether the risk of rescue systemic corticosteroids was due to asthma comorbidity or CRSwNP per se. 6. In the “Implication for future research and clinical practice” section, define “…less severe disease…” either narratively or using scores of the outcomes meta-analyzed. 7. In the “Limitation of the study” section, rephrase “… less severe disease (without asthma)…” because CRSwNP could be severe by itself, even if no other comorbidities co-exist. Moreover, highlight that three of meta-analyzed studies were contacted from the same group. 8. In Table 1 add the mean and range of the ages recruited per study.

REVIEWER	Weatherall, Mark University of Otago Wellington
REVIEW RETURNED	25-Jan-2021

GENERAL COMMENTS	The authors report a systematic review and meta-analysis of a monoclonal antibody for treatment of IgE related nasal polyposis. In the statistical methods generally the software used should be the last sentence. The authors have not stated the method of meta-analysis for the main or any continuous outcomes. It is possible to reproduce the primary analysis using R software (package meta) using the inverse variance method, the DerSimonian-Laird estimator of tau-squared and the Jackson method for its confidence interval. This should be stated explicitly. The handling and discussion of fixed versus random effects is not particularly satisfactory. There are two largish pharma sponsored studies with have most of the information and two smaller studies with effect sizes much larger and much smaller than the two main studies. This is unable to be satisfactorily resolved by a leave one out methodology or by meta-regression. In the Forest plots the order of the studies should be by effect size as an informal graphical method to look for publication bias and the described weights should be the fixed effects weights and not the random effects weights. The strength of evidence for the random effects estimate is modest (and overstated by the authors) with a

	confidence bound very close to the Null. In addition there is no discussion about the MCID for the main outcome variable; that is the effect may be statistically significant but is it scientifically meaningful?

REVIEWER	Haile, Sarah University of Zurich, Epidemiology, Biostatistics and Prevention Institute
REVIEW RETURNED	26-Jan-2021

GENERAL COMMENTS	The statistical methods could be specified more clearly. Was a random or fixed effects model used? (Note: the Cochrane handbook gives some information on choosing between the two, especially point 6, https://training.cochrane.org/handbook/current/chapter-10#section-10-10-4-1) Did you assess publication bias? If you expand your search criteria to include non-English results, could you add any studies? A review of language in the manuscript, including Figure 1 is necessary. The subfigures of Figure 4 are quite small. Is it possible to split this into 2 figures?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Jakub Novosad, University Hospital Hradec Kralove
Comments to the Author:
Dear authors, I have read with particular interest your submitted article covering the very actual issue, a biological therapy of CRSwNP. I found it very understandably and clearly written with logic structure. All used statistical methods are relevant and explained with clarity. I found only some typos (page 12, line 15, PRIMSA). Thank you for a very interesting work!
Reply: We appreciate the reviewer's time and efforts to improve our manuscript for publication. We agree with the reviewer and correct the word "PRIMSA". (Line 88)

Reviewer: 2
Dr. George Konstantinou, 424 General Military Training Hospital
The submitted article is an interesting and well-conducted systematic review and meta-analysis.
Reply: We appreciate the reviewer's time and efforts to improve our manuscript for publication.
Comments to the Author:
In the Methods section:
1. Add the "Minimally Clinically Important Difference" (MCID) for each of the outcomes of interest that were meta-analyzed. This will help the average reader to better appreciate not only the statistical but also the clinical importance of the calculated changes presented in the results.
Reply: We thank the reviewer for the constructive comments. We agree with the reviewer. There was none "Minimally Clinically Important Difference" for each of the outcomes of interest that were meta-analyzed, except SNOT-22. We add the statement as follows.
"There was an improvement of at least the minimal clinically important difference (MCID; ≥8.9 points)." (Lines 174-175)

“Placebo-corrected improvements of SNOT-22 was 15.6 points, which exceeded the commonly accepted MCID of 8.9 points.” (Lines 228-229)

2. Describe in a couple of sentences how the nasal polyp score was calculated, which parameters were assessed in the other outcomes of interest (nasal congestion score and total nasal symptom score), and how the need for surgery was defined.

Reply: We thank the reviewer for the constructive comments. We agree with the reviewer and add the statement as follows.

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

“Nasal congestion score (NCS) was assessed daily by the participant via an electronic diary as the response to the following question: Is your nose blocked? The four available response options were scored from 0 (no symptoms) to 3 (severe symptoms).” (Lines 165-167)

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

“Reduced need for surgery (RNS) through week 24 was defined as achievement of NPS of 4 or lower (≤2 for each nostril).” (Lines 196-197)

3. Was the nasal congestion score based on PROs or VAS in each of the studies included in the meta-analysis?

Reply: We thank the reviewer for the constructive comments. The nasal congestion score was based on PROs and added the statement as follows.

“Nasal congestion score (NCS) was assessed daily by the participant via an electronic diary as the response to the following question: Is your nose blocked? The four available response options were scored from 0 (no symptoms) to 3 (severe symptoms).” (Lines 165-167)

In the “Primary Outcomes” section:

4. Provide the mean change for SNOT-22.

Reply: We thank the reviewer for the constructive comments. We agree with the reviewer and add the statement as follows.

“The mean difference in the change of Sino-Nasal Outcome Test-22 (SNOT-22) score was 15.62 points lower in participants who received omalizumab (MD = -15.62; 95% CI, -19.79 to -11.45; 265 participants; I2 = 0%; Figure 4C).” (Lines 172-173)

5. In the results, explain whether the risk of rescue systemic corticosteroids was due to asthma comorbidity or CRSwNP per se.

Reply: We thank the reviewer for the constructive comments. We agree with the reviewer and add the statement as follows.

“Moreover, patients with asthma are more likely to develop CRSwNP than are those without asthma, and they are more likely to receive more oral corticosteroid courses. Therefore, the risk of RSCS may be due to asthma comorbidity.” (Lines 221-224)

6. In the “Implication for future research and clinical practice” section, define “...less severe disease...” either narratively or using scores of the outcomes meta-analyzed.

Reply: We thank the reviewer for the constructive comments. We agree with the reviewer and add the statement as follows.

“However, it is still unknown that omalizumab is effective in patients with less severe CRSwNP (such as serum IgE level <30 IU/mL and NPS=1 for each nostril or unilateral nostril)” (Lines 234-235)

7. In the “Limitation of the study” section, rephrase “... less severe disease (without asthma)...” because CRSwNP could be severe by itself, even if no other comorbidities co-exist.

Moreover, highlight that three of meta-analyzed studies were contacted from the same group.

Reply: We thank the reviewer for the constructive comments. We agree with the reviewer and add the statement as follows.

“4 RCTs were recruited from the same group with moderate to severe CRSwNP. Therefore, there is no evidence on whether or not patients with less severe CRSwNP (serum IgE level <30 IU/mL and NPS=1 for each nostril or unilateral nostril) would benefit.” (Lines 242-245)
8. In Table 1 add the mean and range of the ages recruited per study.
Reply: We thank the reviewer for the constructive comments. We agreed with the reviewer and revised the Table 1.

Reviewer: 3
Dr. Mark Weatherall, University of Otago Wellington
Comments to the Author:
The authors report a systematic review and meta-analysis of a monoclonal antibody for treatment of IgE related nasal polyposis.
Reply: We thank the reviewer for the constructive comments. We agree with the reviewer and add the statement as follows.
1. In the statistical methods generally the software used should be the last sentence.
Reply: We thank the reviewer for the constructive comments. We agree with the reviewer and put the sentence of software used in the last.
“All meta-analyses were conducted by the Review Manager (version 5.3).” (Lines 133)
2. The authors have not stated the method of meta-analysis for the main or any continuous outcomes.
Reply: We thank the reviewer for the constructive comments. We agree with the reviewer and add the statement as follows.
“For continuous outcomes, a generic inverse-variance method with fixed-effects models was used to calculate pooled mean differences and 95% confidence interval.” (Lines 121-123)
3. It is possible to reproduce the primary analysis using R software (package meta) using the inverse variance method, the DerSimonian-Laird estimator of tau-squared and the Jackson method for its confidence interval. This should be stated explicitly.
Reply: We thank the reviewer for the constructive comments. We agree with the reviewer. The current meta-analysis software includes Review Manager, Stata, and R software. We currently do not understand how to use R software, but after repeating it with the Stata, the result is acquaintance with the current Review Manager. The results were shown in following figures using Stata.

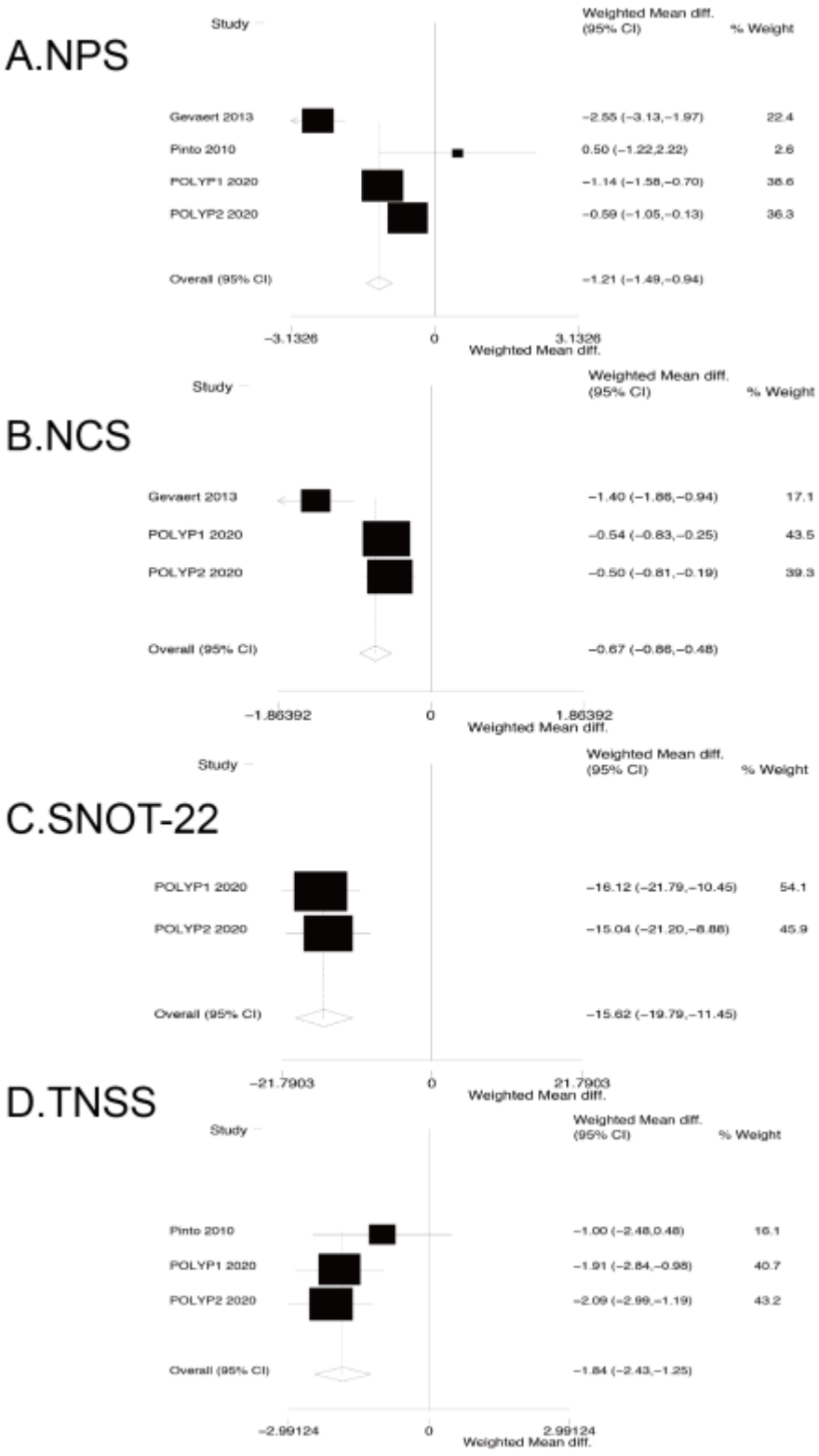

Figure 1. Meta-analyses of omalizumab versus placebo by Stata, comparing efficacy.

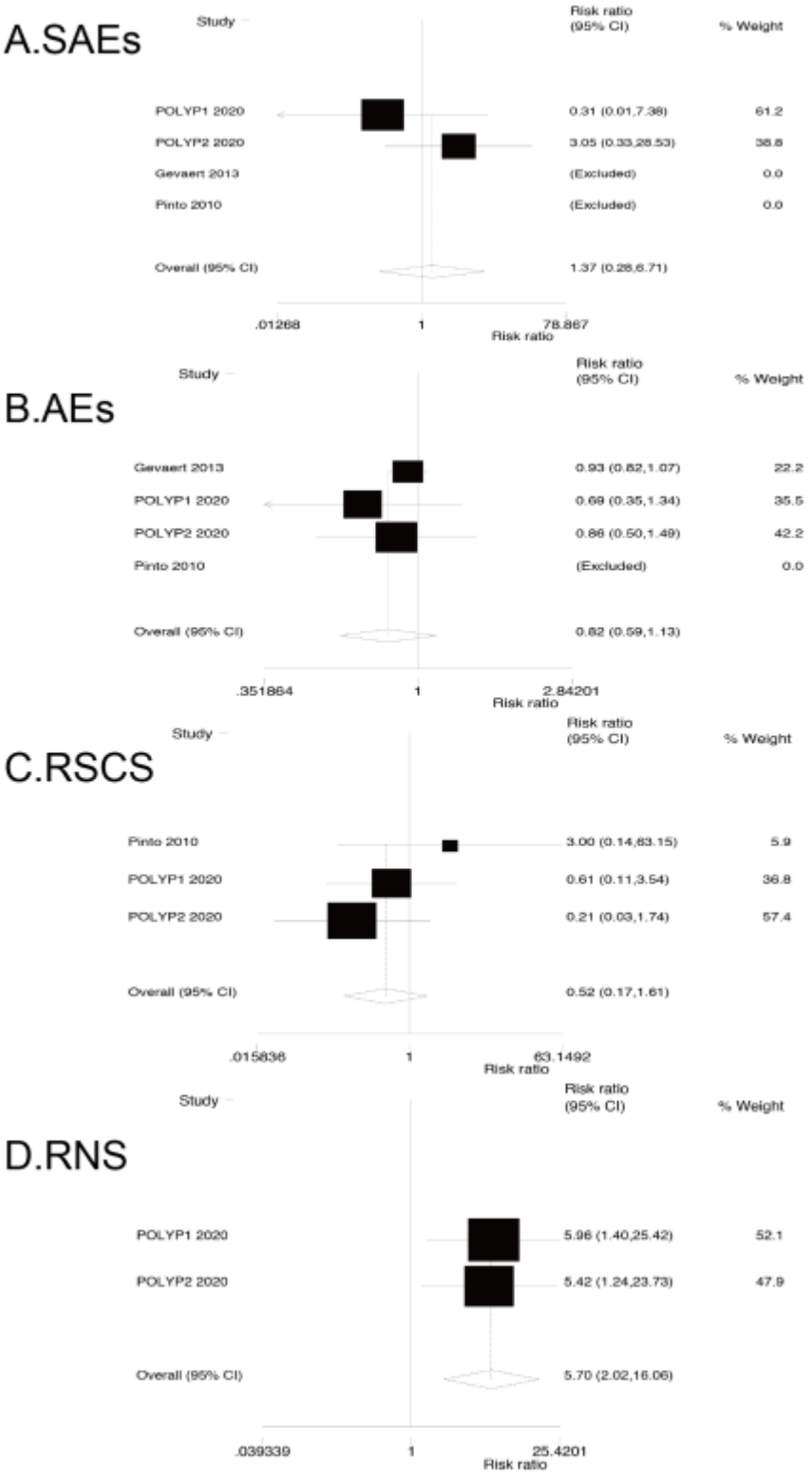

Figure 2. Meta-analyses of omalizumab versus placebo by Stata, comparing efficacy and safety.

4. The handling and discussion of fixed versus random effects is not particularly satisfactory. There are two largish pharma sponsored studies with have most of the information and two smaller studies with effect sizes much larger and much smaller than the two main studies. This is unable to be satisfactorily resolved by a leave one out methodology or by meta-regression. In the Forest plots the order of the studies should be by effect size as an informal graphical method to look for publication

bias and the described weights should be the fixed effects weights and not the random effects weights. The strength of evidence for the random effects estimate is modest (and overstated by the authors) with a confidence bound very close to the Null.
Reply: We thank the reviewer for the constructive comments. We agree with the reviewer and the described weights were chose the fixed effects weights. We add the statement as follows.
“There are two large pharma-sponsored RCTs with most of the information and two smaller RCTs with effect sizes much larger and much smaller than the two main studies. A random-effects meta-analysis will exacerbate the effects of the bias. Therefore, we choose a fixed-effect analysis that will be affected less, although strictly it will also be inappropriate.” (Lines 125-129)
In the Review Manager, the order of the studies were sort by the first letter of the studies’ name. We do not understand how to use R software, so we fail to order the studies by effect size to look for publication bias. In fact, we assessed the publication bias and there existed publication bias as following Figure 3. However, it may be more appropriated to state “There were only 4 RCTs (<10), so a possibility of publication bias was not assessed by constructing a funnel plot in this systematic review.” (Lines 248-250)

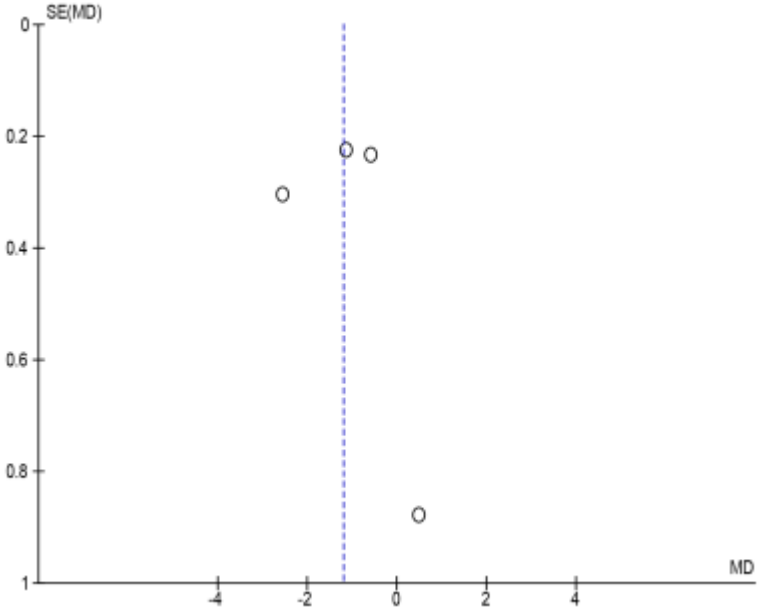

Figure 3. Funnel plot.
5. In addition there is no discussion about the MCID for the main outcome variable; that is the effect may be statistically significant but is it scientifically meaningful?
Reply: We thank the reviewer for the constructive comments. We agree with the reviewer. There was only “Minimally Clinically Important Difference” for SNOT-22. We add the statement as follows.
“Placebo-corrected improvements of SNOT-22 was 15.6 points, which exceeded the commonly accepted MCID of 8.9 points.” (Lines 228-229)

Reviewer: 4
Dr. Sarah Haile, University of Zurich
Comments to the Author:
1. The statistical methods could be specified more clearly. Was a random or fixed effects model used? (Note: the Cochrane handbook gives some information on choosing between the two, especially point 6, https://training.cochrane.org/handbook/current/chapter-10#section-10-10-4-1)
Reply: We thank the reviewer for the constructive comments. We agree with the reviewer and add the statement as follows.

“There are two large pharma-sponsored RCTs with most of the information and two smaller RCTs with effect sizes much larger and much smaller than the two main studies. A random-effects meta-analysis will exacerbate the effects of the bias. Therefore, we choose a fixed-effect analysis that will be affected less, although strictly it will also be inappropriate.” (Lines 125-129)

2. Did you assess publication bias?

Reply: We thank the reviewer for the constructive comments. We agree with the reviewer. In fact, we assessed the publication bias and there existed publication bias as following Figure. However, it may be more appropriated to state “There were only 4 RCTs (<10), so a possibility of publication bias was not assessed by constructing a funnel plot in this systematic review.” (Lines 248-150)

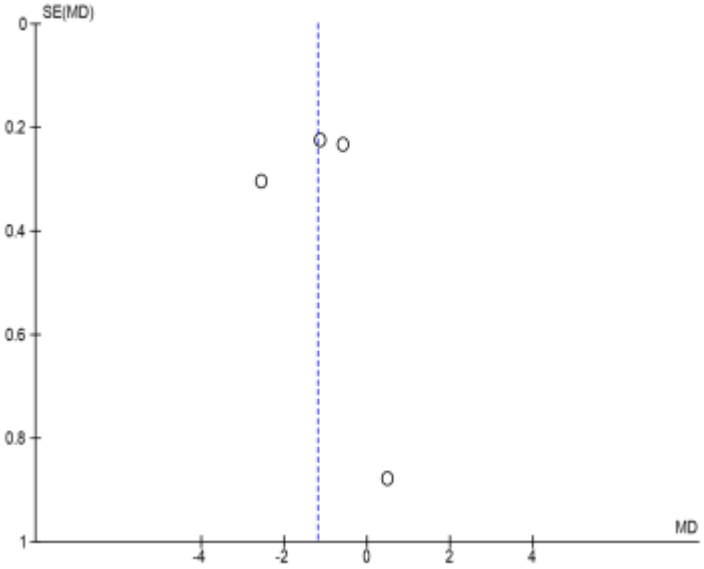

Figure. Funnel plot.

3. If you expand your search criteria to include non-English results, could you add any studies?

Reply: We thank the reviewer for the constructive comments. We agree with the reviewer. In fact, we did not restrict the language when searching, and did not find other non-English studies that could be included.

4. A review of language in the manuscript, including Figure 1 is necessary.

Reply: We thank the reviewer for the constructive comments. We agree with the reviewer and revised the manuscript and Figure 1.

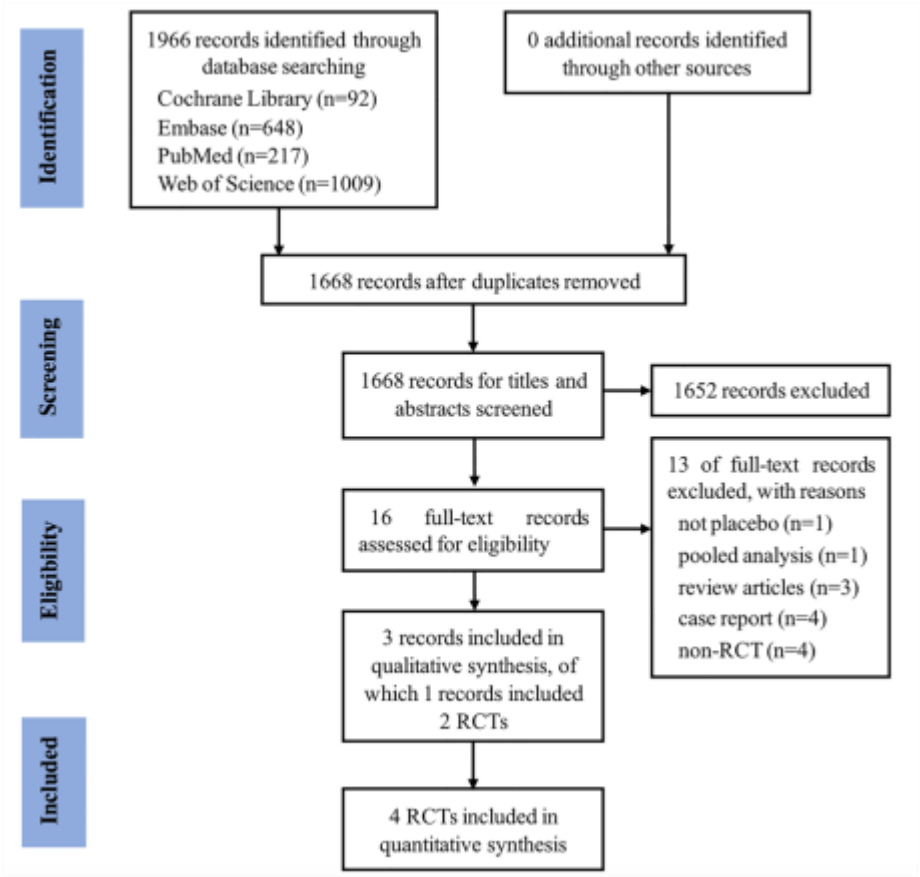

Figure 1. PRISMA flow diagram of the literature search.

5. The subfigures of Figure 4 are quite small. Is it possible to split this into 2 figures?

Reply: We thank the reviewer for the constructive comments. We agree with the reviewer and split Figure 4 into 2 figures (Figure 4 and 5).

That's all for the reply to the editors and reviewers' comments. All the authors have read and approved the revised manuscript.

We greatly appreciate your time and efforts to improve our manuscript for publication and look forward to your response to the changes we have made.

Yours sincerely,

Rui Zheng, MD and Qintai Yang, MD, PhD

Department of Otolaryngology-Head and Neck Surgery, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou 510630, China

VERSION 2 – REVIEW

REVIEWER	Konstantinou, George 424 General Military Training Hospital, Allergy and Clinical Immunology
REVIEW RETURNED	07-Apr-2021

GENERAL COMMENTS	The authors have satisfactorily addressed my comments. They just have to exclude from their revised version the criterion of IgE<30 IU/lt for two reasons: firstly, IgE is not a biomarker of CRSwP severity and secondly, serum IgE level of <30 IU/lt is a contraindication for omalizumab administration.

REVIEWER	Weatherall, Mark University of Otago Wellington
REVIEW RETURNED	30-Mar-2021

GENERAL COMMENTS	The authors have responded to my comments.

REVIEWER	Haile, Sarah University of Zurich, Epidemiology, Biostatistics and Prevention Institute
REVIEW RETURNED	29-Mar-2021

GENERAL COMMENTS	Thank you for your revision. In the methods section, the following sentences were added "There are two large pharma-sponsored RCTs with most of the information and two smaller RCTs with effect sizes much larger and much smaller than the two main studies. A random-effects meta-analysis will exacerbate the effects of the bias. Therefore, we choose a fixed-effect analysis that will be affected less, although strictly it will also be inappropriate. ". This would imply that the methods depended on the results. Please justify the use of fixed effects model independently from results.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4

Dr. Sarah Haile, University of Zurich

Comments to the Author:

Thank you for your revision.

Reply: We appreciate the reviewer's time and efforts to improve our manuscript for publication.

In the methods section, the following sentences were added "There are two large pharma-sponsored RCTs with most of the information and two smaller RCTs with effect sizes much larger and much smaller than the two main studies. A random-effects meta-analysis will exacerbate the effects of the bias. Therefore, we choose a fixed-effect analysis that will be affected less, although strictly it will also be inappropriate. ". This would imply that the methods depended on the results. Please justify the use of fixed effects model independently from results.

Reply: We thank the reviewer for the constructive comments. We agree with the reviewer. "In particular, if results of smaller studies are systematically different from results of larger ones, which can happen as a result of publication bias or within-study bias in smaller studies (Egger et al 1997, Poole and Greenland 1999, Kjaergard et al 2001), then a random-effects meta-analysis will exacerbate the effects of the bias (see also Chapter 13, Section 13.3.5.6). A fixed-effect analysis will be affected less, although strictly it will also be inappropriate." (from the reviewer's note, https://training.cochrane.org/handbook/current/chapter-10#section-10-10-4). Additionally, based on the reviewer 3's comments "There are two largish pharma sponsored studies with have most of the information and two smaller studies with effect sizes much larger and much smaller than the two main studies. This is unable to be satisfactorily resolved by a leave one out methodology or by meta-

regression. In the Forest plots the order of the studies should be by effect size as an informal graphical method to look for publication bias and the described weights should be the fixed effects weights and not the random effects weights.", thus we added the statement "There are two large pharma-sponsored RCTs with most of the information and two smaller RCTs with effect sizes much larger and much smaller than the two main studies. A random-effects meta-analysis will exacerbate the effects of the bias. Therefore, we choose a fixed-effect analysis that will be affected less, although strictly it will also be inappropriate".

Changed from random effects model to fixed effects model, two outcomes (NPS and NCS) were not actually change the nature of the results in our study (Table1) . This meant the use of fixed effects model is independently from results.

Table 1. outcomes by random effects model and fixed effect model

Outcomes	Mean Difference (95% CI)	
	Fixed-effects	Random-effects
NPS	-1.20 [-1.48, -0.92]	-1.11 [-2.09, -0.13]
NCS	-0.67 [-0.86, -0.48]	-0.78 [-1.25, -0.30]

Therefore, we added the reference and stated as follows.

"A random-effects meta-analysis may exacerbate the effects of the bias and a fixed-effect analysis will be affected less, although strictly fixed-effect analysis will also be inappropriate. (reference: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.) Therefore, we choose a fixed-effect analysis in this study." (Lines 127-130)

Reviewer: 3

Dr. Mark Weatherall, University of Otago Wellington

Comments to the Author:

The authors have responded to my comments.

Reply: We appreciate the reviewer's time and efforts to improve our manuscript for publication.

Reviewer: 2

Dr. George Konstantinou, 424 General Military Training Hospital

Comments to the Author:

The authors have satisfactorily addressed my comments. They just have to exclude from their revised version the criterion of IgE<30 IU/lt for two reasons: firstly, IgE is not a biomarker of CRSwP severity and secondly, serum IgE level of <30 IU/lt is a contraindication for omalizumab administration.

Reply: We appreciate the reviewer's time and efforts to improve our manuscript for publication. We agree with the reviewer and exclude the criterion of IgE<30 IU/ml.

The sentence "However, it is still unknown that omalizumab is effective in patients with less severe CRSwNP (such as serum IgE level <30 IU/mL and NPS=1 for each nostril or unilateral nostril) and more affordable compared to conventional treatment with topical and systemic corticosteroids and surgery." was change into "However, it is still unknown that omalizumab is effective in patients with less severe CRSwNP (such as NPS=1 for each nostril or unilateral nostril) and more affordable compared to conventional treatment with topical and systemic corticosteroids and surgery." (Line 234-237)

The sentence "Therefore, there is no evidence on whether or not patients with less severe CRSwNP (serum IgE level <30 IU/mL and NPS=1 for each nostril or unilateral nostril) would benefit." was change into "Therefore, there is no evidence on whether or not patients with less severe CRSwNP (NPS=1 for each nostril or unilateral nostril) would benefit." (Lines 244-246)

That's all for the reply to the reviewers' comments. All the authors have read and approved the revised manuscript.

We greatly appreciate your time and efforts to improve our manuscript for publication and look forward to your response to the changes we have made.

Yours sincerely,

Rui Zheng, MD and Qintai Yang, MD, PhD

Department of Otolaryngology-Head and Neck Surgery, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou 510630, China