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The effectiveness of biologics for patients with severe asthma: study protocol for an umbrella review of systematic reviews and meta-analyses

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Manuscripts

The effectiveness of biologics for patients with severe asthma: study protocol for an umbrella review of systematic reviews and meta-analyses

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ABSTRACT

Introduction: Many systematic reviews and meta-analyses (SRs/MAs) have evaluated the efficacy of biologic therapies for severe asthma. However, the overall quality of these SRs/MAs are unclear, which may influence the selection of biologics and lead to misleading clinical decision. This umbrella review aims to objectively evaluate the overall quality of these SRs/MAs and reassess the efficacy of biologic therapy for severe asthma. Thus, this study will provide reliable evidence for clinical practice.

Methods and analysis: A systematic search will be performed in PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus databases. Literature screening and data extraction will be conducted according to inclusion and exclusion criteria. Then, we will evaluate the reporting quality,

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4 23 methodological quality and evidence quality of these SRs/MAs using Preferred Reporting Items for
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6 24 Systematic Review and Meta-Analysis (PRISMA) statement, A Measurement Tool to Assess
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9 25 Reviews (AMSTAR) 2, and Grading of Recommendation Assessment, Development and Evaluation
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11
12 26 (GRADE) system, respectively. In addition, the re-meta-analysis of outcomes will be performed
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14 27 applying R 4.3.3.

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17 28 **Ethics and dissemination:** Since this umbrella review will use publicly available data, ethics
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20 29 approval is not required. We will disseminate the results of this study through a peer-reviewed
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22 30 journal.

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25 31 **PROSPERO registration number:** CRD42024607393.

26
27 32 **Keywords:** biologics, severe asthma, umbrella review, protocol

30 33 **Article Summary**

32 34 **Strengths and limitations of this study**

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35 35 (1)This study is the first umbrella review of systematic reviews and meta-analyses (SRs/MAs)
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37
38 36 evaluating the efficacy of biologic therapy for patients with severe asthma.

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40 37 (2)This umbrella review will objectively evaluate the overall quality of eligible SRs/MAs.

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43 38 (3)Only articles in English will be included in this study and important studies published in other
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45
46 39 languages may be omitted.

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48 40 (4)Some subjective factors may have an effect on the evaluation of literature quality.

50 41 **1 INTRODUCTION**

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53 42 Asthma is a prevalent chronic respiratory disease characterized by chronic airway inflammation and
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56 43 airway hyperresponsiveness. It often has recurrent wheezing, shortness of breath, chest tightness,
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59 44 cough and other symptoms.^[1] Asthma is a serious global health problem, affecting about 300 million
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4 45 people worldwide and causing about 250,000 deaths annually.^[2] What's worse, patients with severe
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7 46 asthma have more severe symptoms, more frequent exacerbations, and more serious medication side
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10 47 effects, which can interfere with patient's daily life, sleep, and physical activity.^[3] A Dutch study
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12 48 showed that about 3.7% of people with asthma have severe asthma.^[4] In addition, severe asthma
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15 49 leads to very high medical costs. In a Canadian study, severe asthma accounts for more than 60% of
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17 50 the cost of asthma.^[5]

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20 51 Severe asthma means patients that remain uncontrolled despite adhering to maximal optimized
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22 52 high-dose inhaled corticosteroids (ICS)/long-acting beta-agonists(LABA) treatment and management
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24
25 53 of associated factors, or that worsen when high-dose treatment is decreased.^[6] For these patients,
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27 54 add-on therapy, mainly emerging biologics, are needed to provide new hope for the treatment of
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30 55 severe asthma. Biologics can block the immuno-inflammatory cascade in the pathological course of
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33 56 severe asthma by precisely targeting inflammatory cytokines.^[6] Biologics for severe asthma mainly
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35 57 include anti-immunoglobulin E (anti-IgE) treatment (omalizumab), anti-interleukin-5/5R α
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38 58 (anti-IL5/5R α) treatment (mepolizumab, reslizumab, benralizumab), anti-interleukin-4R α
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40 59 (anti-IL4R α) treatment (dupilumab), and anti-thymic stromal lymphopoietin (anti-TSLP) treatment
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43 60 (tezepelumab). In previous studies, biologics have been shown to be beneficial for severe asthma,
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45
46 61 which can reduce the frequency of acute exacerbations and hospitalization, improve lung function
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48 62 and quality of life, and decrease the use of systemic corticosteroids.^{[7][8][9]}

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51 63 Recently, there are many systematic reviews and meta-analyses (SRs/MAs) have shown the efficacy
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53 64 of biologics for severe asthma. Nevertheless, it was also mentioned in the SRs/MAs that the
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56 65 reliability of the results may be affected by the heterogeneity among studies and other risks of bias.
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59 66 Methodological quality, reporting quality and evidence quality of these SRs/MAs are still unclear.
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4 67 The umbrella review can evaluate the overall quality of relevant SRs/MAs in detail, providing
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6 68 high-quality evidence for clinical practice. However, no umbrella reviews or overviews on this topic
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9 69 have been found. Therefore, it is necessary to conduct an umbrella review to evaluate and summarize
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12 70 the published SRs/MAs.

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14 71 In this umbrella review, the reporting quality, methodological quality and evidence quality of
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17 72 relevant SRs/MAs will be evaluated through applying Preferred Reporting Items for Systematic
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20 73 Review and Meta-Analysis (PRISMA) statement, A Measurement Tool to Assess Reviews
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22 74 (AMSTAR) 2, and Grading of Recommendation Assessment, Development and Evaluation
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24
25 75 (GRADE) system, respectively. Meanwhile, we will reassess the efficacy of biologics for patients
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27 76 with severe asthma. Ultimately, this study is expected to provide evidence-based medical evidence
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30 77 for the application of biologics for severe asthma.

31 32 78 **2 METHODS AND ANALYSIS**

33 34 35 79 **2.1 Design and registration**

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38 80 This protocol is registered in PROSPERO (Registration number: CRD42024607393). The date of
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41 81 first version is October 29, 2024. It will be reported according to Preferred Reporting Items for
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43 82 Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.^[10] The detailed
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46 83 PRISMA-P checklist can be found in **Supplementary file 1**. This study is commenced on November
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48 84 15, 2024 and will complete before May 31, 2025.

49 50 51 85 **2.2 Inclusion criteria**

52 53 86 **2.2.1 Types of participants**

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56 87 This umbrella review will consider SRs/MAs that focus on participants over 12 years old with severe
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59 88 asthma. The criteria for severe asthma will refer to the 2024 Global Initiative for Asthma (GINA).^[6]
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2.2.2 Types of interventions

The interventions of this study include biologic therapy with/without routine therapy. Biologic therapy recommended by 2024 GINA are as follows: anti-IgE treatment (omalizumab), anti-IL5/5R α treatment (mepolizumab, reslizumab, benralizumab), anti-IL4R α treatment (dupilumab), and anti-TSLP treatment (tezepelumab).^[6]

2.2.3 Types of comparisons

The control group will be given routine therapy or corresponding placebos.

2.2.4 Types of outcomes

The literature are required to report 1 or more of the following outcomes: annualized asthma exacerbation rate (AER), the change from baseline in pre-bronchodilator forced expiratory volume in 1second (pre-BD FEV1), asthma control questionnaire (ACQ), asthma control test (ACT), asthma quality of life questionnaire (AQLQ), number of hospitalizations due to asthma, number of eosinophils in blood, and fractional exhaled nitric oxide (FeNO).

Moreover, we will collect the information of adverse events and severe adverse events caused by biologic therapy. Thus, we can evaluate the safety of biologics on patients with asthma.

2.2.5 Types of studies

This study will only include eligible SRs/MAs for analysis.

2.3 Exclusion criteria

(1) Articles which the full text is not available, (2)Articles without available data, (3) Duplicate or retracted studies, (4) Articles in a language other than English.

2.4 Search strategy

Two authors (QX and BX) will independently carry out the retrieval of literature. PubMed,

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4 111 EMBASE, Cochrane Library, Web of Science, and Scopus databases will be searched for literature.
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7 112 We will also review the conference proceedings. The searched period will run from the date of
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9 113 establishment of databases until November 15, 2024. The search terms are showed as follows:
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11
12 114 “Mepolizumab”, “Reslizumab”, “Benralizumab”, “Omalizumab”, “Dupilumab”, “Tezepelumab”,
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14 115 “Asthma”, “systematic review”, and “meta-analysis”. The search strategy in PubMed database are
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17 116 listed in **Table 1**. The full search strategy are provided in **Supplementary file 2**.

18
19
20 117 Table 1 Search strategy in PubMed

No	Search terms
#1	((((((((((Mepolizumab[MeSH Terms]) OR (Mepolizumab[Title/Abstract]) OR (SB-240563[Title/Abstract])) OR (SB240563[Title/Abstract])) OR (Nucala[Title/Abstract])) OR (Bosatria[Title/Abstract])) OR ((((((((((Reslizumab[MeSH Terms]) OR (Reslizumab[Title/Abstract]) OR (Cinqair[Title/Abstract])) OR (SCH-55700[Title/Abstract])) OR (SCH 55700[Title/Abstract])) OR (SCH55700[Title/Abstract])) OR (DCP-835[Title/Abstract])) OR (DCP 835[Title/Abstract])) OR (DCP835[Title/Abstract])) OR (CEP-38072[Title/Abstract])) OR (CEP38072[Title/Abstract])) OR (((((Benralizumab[MeSH Terms]) OR (Benralizumab[Title/Abstract]) OR (MEDI-563[Title/Abstract])) OR (MEDI 563[Title/Abstract])) OR (Fasenra[Title/Abstract])) OR (BIW-8405[Title/Abstract])) OR ((Omalizumab[MeSH Terms]) OR (Xolair[Title/Abstract])) OR ((((((Dupilumab[MeSH Terms]) OR (Dupilumab[Title/Abstract]) OR (SAR231893[Title/Abstract])) OR (SAR-231893[Title/Abstract])) OR (REGN668[Title/Abstract])) OR (REGN-668[Title/Abstract])) OR (Dupixent[Title/Abstract])) OR (((((((Tezepelumab[MeSH Terms]) OR (Tezepelumab[Title/Abstract]) OR (MEDI-9929[Title/Abstract])) OR (MEDI9929[Title/Abstract])) OR (MEDI-19929[Title/Abstract])) OR (AMG-157[Title/Abstract])) OR (tezspire[Title/Abstract]) OR (tezepelumab-ekko[Title/Abstract]))

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4 #2 (((Asthma[MeSH Terms]) OR (Asthmas[Title/Abstract])) OR (Asthma, Bronchial[Title/Abstract])) OR (Bronchial
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6 Asthma[Title/Abstract]))
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9 #3 (((((((((((Meta-Analysis as Topic[MeSH Terms]) OR (Meta Analysis[Publication Type])) OR (meta
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11 analysis[Title/Abstract])) OR (meta analyses[Title/Abstract])) OR (meta-analysis[Title/Abstract])) OR
12
13 (meta-analyses[Title/Abstract])) OR (data pooling[Title/Abstract])) OR (data poolings[Title/Abstract])) OR
14
15 (clinical trial overview[Title/Abstract])) OR (clinical trial overviews[Title/Abstract])) OR (systematic
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17 review[Title/Abstract])) OR (systematic reviews[Title/Abstract]))
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22 #4 #1 AND #2 AND #3
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25 118 2.5 Study selection

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27 119 After duplicate removal, two reviewers (QX and YH) will individually examine the titles and
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29 abstracts of eligible articles that meet the inclusion and exclusion criteria, and exclude irrelevant
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31 studies. EndNote 20 software will be applied to generate citations and remove duplicate articles.^[11]
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35 122 Then, two authors (QX and YH) will independently review the full texts of remaining articles and
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37 determine the final studies included in umbrella review. All disagreements will be resolved by the
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39 third independent author (MW). The process of selecting studies is illustrated in **Figure 1**.
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43 125 2.6 Data extraction

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45 126 Data extraction will be conducted by two researchers (BX and YH). We will extract information
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47 from eligible SRs/MAs.
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51 128 The extracted information of SRs/MAs include name of first author, year of publication, title of
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53 129 SRs/MAs, country, database searched, number of clinical studies, sample size per group, duration of
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55 disease, average age per group, gender ratio per group, type and dose of biologics, treatment
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57 duration, type of comparisons, efficacy and safety outcomes, type of effect sizes, effect sizes for
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4 132 efficacy and safety outcomes, heterogeneity, and publication bias. Any discrepancies will be
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7 133 resolved by discussion.

9 134 **2.7 Quality assessment**

12 135 2.7.1 Reporting quality assessment

14 136 The reporting quality of the included SRs/MAs will be evaluated through PRISMA statement.^[12] It
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17 137 consists of 27 items and is scored as follows. A complete report is worth 1 point, a partial report is
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20 138 worth 0.5 points, and an incomplete report is worth 0 points. The total score of PRISMA statement is
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22 139 27 points. In the final evaluation, a score of ≤ 15 indicates that the report have relatively serious
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25 140 information defects, a score of 15.5 ~ 21 indicates that the report have some defects, and a score of
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27 141 21.5 ~ 27 indicates that the report is relatively complete.

30 142 2.7.2 Methodological quality assessment

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33 143 In this umbrella review, we will assess the methodological quality of included SRs/MAs using the
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35 144 AMSTAR 2 tool.^[13] It includes 16 items, with 7 key items. The AMSTAR 2's development team
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38 145 recommended focusing on the methodological conditions of key items and giving an overall
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40 146 evaluation. Each item has the following options: yes, partial yes, no. Methodological quality of each
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43 147 SRs/MAs will be categorized as high, moderate, low and critically low.

46 148 2.7.3 Quality of evidence assessment

48 149 In terms of quality of evidence, we will apply the GRADE system to assess in detail.^{[14][15]} It will be
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51 150 classified into four grades: high, moderate, low, and critically low. The upgrading factors of the
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53 151 quality of evidence include large effect size, residual confounding, and dose-response relationship,
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56 152 while the degrading factors include limitations of the study, inconsistency, indirectness, publication
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59 153 bias, and imprecision.

2.8 Statistical analysis

All analyses will be conducted through “meta” package in R 4.3.3 software. Outcomes will be expressed as mean difference (MD) and risk ratio (RR) with corresponding 95% confidence intervals (CIs). Firstly, we will assess the heterogeneity of included studies by using the Cochrane’s Q test and I^2 statistics.^[16] $P < 0.1$ or $I^2 > 40\%$ indicates significant heterogeneity, and the random-effects model will be used.^[17] Or else, we will choose fixed-effects model. Then, we will calculate pooled MDs or RRs with 95% CIs for each outcome of different biologics. The results will be presented clearly by texts, tables and figures. $P < 0.05$ indicates statistically significant.

In addition, subgroup analysis will be conducted to explore the potential source of heterogeneity.

The publication bias will be evaluated through the funnel plot and the Egger’s test.

3 DISCUSSION

In recent years, many SRs/MAs have emerged. Meanwhile, problems arising from SRs/MAs have also increased. Different study populations and types of studies in included original articles, and varying degrees of methodological defects in SRs/MAs, may lead to misleading clinical decision. As the latest evidence-based medicine analysis method, the umbrella review based on SRs/MAs provides a reliable evidence for clinical practice and makes up the defects of SRs/MAs to some extent.^[18]

Asthma is a serious global health problem, and people with severe asthma have more severe symptoms, frequent exacerbations, and medical economy burden.^[19] In previous SRs/MAs, biologics have good efficacy and safety,^{[20][22]} and are considered as the promising treatment for severe asthma. Nevertheless, the overall quality of these SRs/MAs are still unclear, urging us to conduct an umbrella review. The results of this review will further improve the evidence-based medical basis for

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4 176 the application of biologics for severe asthma and provide a reference for clinical practice.
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6
7 177 However, this study has some limitations. Firstly, only articles in English will be included in this
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9 178 study and important studies published in other languages may be omitted. Secondly, some subjective
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11
12 179 factors may have an effect on the evaluation of literature quality. We will minimize the interference
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14
15 180 of other factors as much as possible and evaluate the quality of literature according to standards.
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17 181 **PATIENT AND PUBLIC INVOLVEMENT**

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20 182 Patients and public will not participate in the design and implementation of the study. The research
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22 183 results will be made available to the patient and public.
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24 25 184 **ETHICS AND DISSEMINATION**

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27 185 Since this study will use publicly available data, ethics approval is not required. We will disseminate
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29
30 186 the results of this review through a peer-reviewed journal.
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32 33 187 **Author affiliations**

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45 46 192 **Author contributions**

47
48 193 QX designed the study, submitted the registration to PROSPERO, and wrote the manuscript. QX and
49
50
51 194 BX completed the search strategy. QX and YH revised the language. MW is responsible for directing
52
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54 195 the overall study. All authors approved the manuscript.
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7 199 (82474483), Science and Technology Innovation Team of Colleges and Universities of
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9 200 Henan Province (23IRTSTHN027), Special Research Fund of National Traditional Chinese
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12 201 Medicine Clinical Research Base (2022JDZX046), and Project of Science and Technology of
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14 202 Henan Province (232102310472).

17 203 **Competing interests**

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19
20 204 None declared.

22 205 **Patient and public involvement**

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25 206 Patients and the public will not involve in the design, or implementation, or report, or dissemination
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27 207 plans of this review.

30 208 **Patient consent for publication**

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33 209 Not applicable.

35 210 **Provenance and peer review**

36
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38 211 Not commissioned; externally peer reviewed.

40 212 **Data availability statement**

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43 213 After completing the study, data are available from corresponding author.

45 214 **Supplemental material**

46
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48 215 The details of the PRISMA-P checklist and the search strategy can be viewed in Supplemental
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51 216 material.

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35 276 **Figure Legends**

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38 277 Figure 1 Flow chart diagram of study selection.
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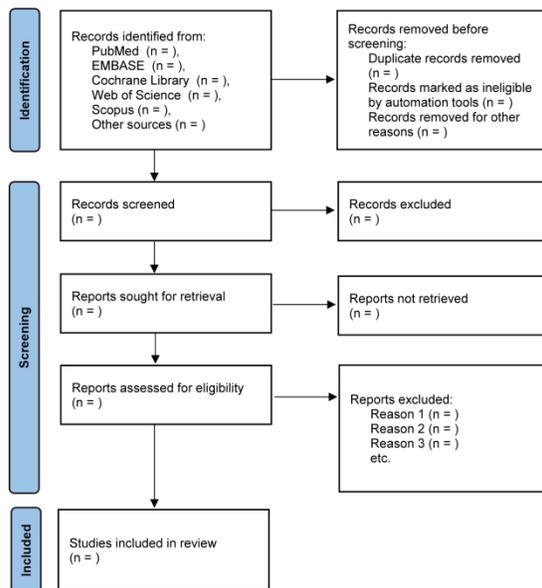


Figure 1 Flow chart diagram of study selection.

210x297mm (300 x 300 DPI)

Supplementary file 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 Checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10-11
Sponsor	5b	Provide name for the review funder and/or sponsor	10-11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	10-11
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-6

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits such that it could be repeated	5-6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), pre-planned data assumptions and simplifications	4-5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary file 2. The details of the search strategy.

Pubmed
<p>((((((((Mepolizumab[MeSH Terms]) OR (SB-240563[Title/Abstract])) OR (SB240563[Title/Abstract])) OR (Nucala[Title/Abstract])) OR (Bosatria[Title/Abstract])) OR</p>
<p>((((((((Reslizumab[MeSH Terms]) OR (Cinqair[Title/Abstract])) OR (SCH-55700[Title/Abstract])) OR (SCH 55700[Title/Abstract])) OR (SCH55700[Title/Abstract])) OR (DCP-835[Title/Abstract])) OR (DCP 835[Title/Abstract])) OR (DCP835[Title/Abstract])) OR (CEP-38072[Title/Abstract])) OR (CEP38072[Title/Abstract])) OR</p>
<p>(((Benralizumab[MeSH Terms]) OR (MEDI-563[Title/Abstract])) OR (MEDI 563[Title/Abstract])) OR (Fasenra[Title/Abstract])) OR (BIW-8405[Title/Abstract])) OR</p>
<p>((Omalizumab[MeSH Terms]) OR (Xolair[Title/Abstract])) OR</p>
<p>((((((Dupilumab[MeSH Terms]) OR (SAR231893[Title/Abstract])) OR (SAR-231893[Title/Abstract])) OR (REGN668[Title/Abstract])) OR (REGN-668[Title/Abstract])) OR (Dupixent[Title/Abstract])) OR</p>
<p>((((((Tezepelumab[MeSH Terms]) OR (MEDI-9929[Title/Abstract])) OR (MEDI9929[Title/Abstract])) OR (MEDI-19929[Title/Abstract])) OR (AMG-157[Title/Abstract])) OR (tezspire[Title/Abstract])) OR (tezpelumab-ekko[Title/Abstract])) AND</p>
<p>(((Asthma[MeSH Terms]) OR (Asthmas[Title/Abstract])) OR (Asthma, Bronchial[Title/Abstract])) OR (Bronchial Asthma[Title/Abstract])) AND</p>
<p>((((((((((((Meta-Analysis as Topic[MeSH Terms]) OR (Meta Analysis[Publication Type])) OR (meta analysis[Title/Abstract])) OR (meta analyses[Title/Abstract])) OR (meta-analysis[Title/Abstract])) OR (meta-analyses[Title/Abstract])) OR (data pooling[Title/Abstract])) OR (data poolings[Title/Abstract])) OR (clinical trial overview[Title/Abstract])) OR (clinical trial overviews[Title/Abstract])) OR (systematic review[Title/Abstract])) OR (systematic reviews[Title/Abstract]))</p>

Embase
#1 'asthma'/exp
#2 'asthma'
#3 'asthma bronchiale' OR 'asthma pulmonale' OR 'asthma, bronchial' OR 'asthmatic' OR 'asthmatic subject' OR 'bronchial asthma' OR 'bronchus asthma' OR 'chronic asthma' OR 'lung allergy'
#4 #1 OR #2 OR #3
#5 'mepolizumab'/exp
#6 'mepolizumab'
#7 'bat 2606' OR 'bat2606' OR 'bosatria' OR 'nucala' OR 'sb 240563' OR 'sb-240563' OR 'sb240563'
#8 'reslizumab'/exp
#9 'reslizumab'
#10 'cep 38072' OR 'cep38072' OR 'cinqaero' OR 'cinqair' OR 'dcp 835' OR 'dcp835' OR 'sch 55700' OR 'sch55700'
#11 'benralizumab'/exp
#12 'benralizumab'
#13 'biw 8405' OR 'biw8405' OR 'fasenra' OR 'khk 4563' OR 'khk4563' OR 'medi 563' OR 'medi563'
#14 'omalizumab'/exp
#15 'omalizumab'
#16 'aomaishu' OR 'cmab 007' OR 'cmab007' OR 'fb 317' OR 'fb317' OR 'gbr 310' OR 'gbr310' OR 'genolair' OR 'gnr 044' OR 'gnr044' OR 'hu 901' OR 'hu901' OR 'monoclonal antibody E 25' OR 'monoclonal antibody E25' OR 'olizumab' OR 'omalizumab alfa' OR 'omalizumab alpha' OR 'omlyclo' OR 'rg 3648' OR 'rg3648' OR

'rhumab 25' OR 'rhumab e25' OR 'sti 004' OR 'sti004' OR 'syn 008' OR 'syn008' OR 'tev 45779' OR 'tev45779' OR 'xolair'

#17 'dupilumab'/exp

#18 'dupilumab'

#19 'bat 2406' OR 'bat2406' OR 'dupixent' OR 'regn 668' OR 'regn668' OR 'sar 231893' OR 'sar231893'

#20 'tezepelumab'/exp

#21 'tezepelumab'

#22 'amg 157' OR 'amg157' OR 'medi 9929' OR 'medi9929' OR 'tezepelumab ekko' OR 'tezepelumab-ekko' OR 'tezspire'

#23 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22

#24 #4 AND #23

Cochrane Library

#1 MeSH descriptor: [Mepolizumab] explode all trees

#2 MeSH descriptor: [Reslizumab] explode all trees

#3 MeSH descriptor: [Benralizumab] explode all trees

#4 MeSH descriptor: [Omalizumab] explode all trees

#5 Xolair

#6 MeSH descriptor: [Dupilumab] explode all trees

#7 MeSH descriptor: [Tezepelumab] explode all trees

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 MeSH descriptor: [Asthma] explode all trees

#10	Asthma, Bronchial
#11	Asthmas
#12	Bronchial Asthma
#13	#9 OR #10 OR #11 OR #12
#14	#8 AND #13
Web of Science	
TS = (Mepolizumab OR Reslizumab OR Benralizumab OR Omalizumab OR Dupilumab OR Tezepelumab) AND TS = (Asthma)	
Scopus	
(TITLE-ABS-KEY (asthma)) AND ((TITLE-ABS-KEY (mepolizumab) OR TITLE-ABS-KEY (reslizumab) OR TITLE-ABS-KEY (benralizumab) OR TITLE-ABS-KEY (omalizumab) OR TITLE-ABS-KEY (dupilumab) OR TITLE-ABS-KEY (tezepelumab)))	

BMJ Open

The effectiveness of biologics for patients with severe asthma: study protocol for an umbrella review of systematic reviews and meta-analyses

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2024-096874.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Mar-2025
Complete List of Authors:	Xiao, Qionghua; The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, National Regional Medical Center of TCM (Pulmonary Disease); Henan University of Chinese Medicine, The First Clinical Medical School Xue, Bingyu; The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, National Regional Medical Center of TCM (Pulmonary Disease); Henan University of Chinese Medicine, The First Clinical Medical School Huang, Yuanming; The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, National Regional Medical Center of TCM (Pulmonary Disease); Henan University of Chinese Medicine, The First Clinical Medical School Wang, Minghang; The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, National Regional Medical Center of TCM (Pulmonary Disease)
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Respiratory medicine
Keywords:	Asthma < THORACIC MEDICINE, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, RESPIRATORY MEDICINE (see Thoracic Medicine)

SCHOLARONE™
Manuscripts

The effectiveness of biologics for patients with severe asthma: study protocol for an umbrella review of systematic reviews and meta-analyses

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ABSTRACT

Introduction: Many systematic reviews and meta-analyses (SRs/MAs) have evaluated the efficacy of biologic therapies for severe asthma. However, the overall quality of these SRs/MAs is unclear, which may influence the selection of biologics and lead to misleading clinical decisions. This umbrella review aims to objectively evaluate the overall quality of these SRs/MAs and reassess the efficacy of biologic therapy for severe asthma. Thus, this study will provide reliable evidence for clinical practice.

Methods and analysis: A systematic search will be performed in PubMed, EMBASE, Cochrane Library, Web of Science, Scopus, and conference abstracts up to March 1, 2025. Literature screening and data extraction will be conducted according to predefined inclusion and exclusion criteria. We

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3
4 23 will evaluate the reporting quality, methodological quality and evidence quality of these SRs/MAs
5
6 24 using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020
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9 25 statement, A Measurement Tool to Assess Systematic Reviews (AMSTAR) 2, and Grading of
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11
12 26 Recommendations Assessment, Development, and Evaluation (GRADE) system, respectively.
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14 27 Additionally, the re-meta-analysis of outcomes will be performed using R software (version 4.3.3).

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16
17 28 **Ethics and dissemination:** Since this umbrella review will use publicly available data, ethics
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19
20 29 approval is not required. The results of this study will be disseminated through publication in a
21
22 30 peer-reviewed journal.

23
24
25 31 **PROSPERO registration number:** CRD42024607393.

26
27 32 **Keywords:** biologics, severe asthma, umbrella review, protocol

28 29 33 **Article Summary**

30 34 **Strengths and limitations of this study**

31
32 35 (1) This study is the first umbrella review of systematic reviews and meta-analyses (SRs/MAs) that
33
34
35 36 evaluate the efficacy of biologic therapy for patients with severe asthma.

36
37 37 (2) This umbrella review will objectively evaluate the overall quality of eligible SRs/MAs.

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39 38 (3) Only articles in English will be included in this study, which may result in the exclusion of
40
41
42 39 potentially relevant studies published in other languages.

43
44 40 (4) Potential subjective bias may influence the evaluation of literature quality.

45 46 41 **1 INTRODUCTION**

47
48 42 Asthma is a prevalent chronic respiratory disease characterized by airway inflammation and airway
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51 43 hyperresponsiveness. It often presents with recurrent wheezing, shortness of breath, chest tightness,
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53
54 44 cough, and other symptoms.^[1] Asthma is a serious global health problem, affecting about 300 million
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4 45 people worldwide and causing about 250,000 deaths annually.^[2] Additionally, and more importantly,
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7 46 patients with severe asthma have more significant symptoms, more frequent exacerbations, and more
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10 47 serious adverse effects of medications, which can interfere with patients' daily life, sleep, and
11
12 48 physical activity.^[3] A Dutch study reported that about 3.7% of people with asthma suffer from severe
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14 49 asthma.^[4] Furthermore, severe asthma is associated with higher healthcare expenditures. A Canadian
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16
17 50 study demonstrated that severe asthma accounts for over 60% of total asthma-related costs.^[5]

18
19
20 51 Severe asthma refers to patients who remain uncontrolled despite adhering to maximal optimized
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22 52 high-dose inhaled corticosteroids (ICS)/long-acting beta-agonists (LABA) treatment and
23
24
25 53 management of associated factors, or who worsen when high-dose treatment is decreased.^[6] For
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27 54 these patients, add-on therapy, mainly emerging biologics, are needed to provide new hope for the
28
29
30 55 treatment of severe asthma. Biologics can modulate the immuno-inflammatory cascade in the
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32
33 56 pathological course of severe asthma by precisely targeting inflammatory cytokines.^[6] Biologics for
34
35 57 severe asthma mainly include anti-immunoglobulin E (anti-IgE) treatment (e.g., omalizumab),
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37
38 58 anti-interleukin-5/5R α (anti-IL-5/5R α) treatment (e.g., mepolizumab, reslizumab, benralizumab),
39
40 59 anti-interleukin-4R α (anti-IL-4R α) treatment (e.g., dupilumab), and anti-thymic stromal
41
42
43 60 lymphopoietin (anti-TSLP) treatment (e.g., tezepelumab). In previous studies, biologics have been
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45
46 61 shown to be beneficial for severe asthma, which can reduce the frequency of acute exacerbations and
47
48 62 hospitalizations, improve lung function and quality of life, and decrease reliance on systemic
49
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51 63 corticosteroids.^{[7][8][9]}

52
53 64 Recently, numerous systematic reviews and meta-analyses (SRs/MAs) have demonstrated the
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56 65 efficacy of biologics for severe asthma. However, these SRs/MAs also highlighted potential
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59 66 limitations. The reliability of the results may be affected by the heterogeneity among studies and
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4 67 other risks of bias. The methodological, reporting, and evidence quality of these SRs/MAs remain
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6
7 68 unclear. The umbrella review can evaluate the overall quality of relevant SRs/MAs in detail, thereby
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9 69 providing high-quality evidence for clinical practice. To date, no umbrella reviews have been
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11
12 70 published on this topic, underscoring the need for this study to synthesize existing evidence.

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14 71 In this umbrella review, the reporting, methodological, and evidence quality of relevant SRs/MAs
15
16
17 72 will be evaluated through using Preferred Reporting Items for Systematic Reviews and
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19
20 73 Meta-Analyses (PRISMA) 2020 statement, A Measurement Tool to Assess Systematic Reviews
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22 74 (AMSTAR) 2, and Grading of Recommendations Assessment, Development, and Evaluation
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24
25 75 (GRADE) system, respectively. Additionally, we will re-evaluate the efficacy of biologics for
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27 76 patients with severe asthma. Ultimately, this study aims to provide evidence-based medical analysis
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29
30 77 and summary for the use of biologics in severe asthma.

31 32 78 **2 METHODS AND ANALYSIS**

33 34 35 79 **2.1 Design and registration**

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37
38 80 This protocol was registered in PROSPERO (Registration number: CRD42024607393). The initial
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41 81 version was registered on October 29, 2024. It will be reported according to Preferred Reporting
42
43 82 Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 statement.^[10] The
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45
46 83 detailed PRISMA-P 2015 checklist can be found in **Supplementary File 1**. This study commenced
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48 84 on November 15, 2024, and is expected to be completed by May 31, 2025.

49 50 51 85 **2.2 Inclusion criteria**

52 53 86 **2.2.1 Types of participants**

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55
56 87 This umbrella review will consider SRs/MAs that focus on participants over 12 years old with severe
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58
59 88 asthma. The criteria for severe asthma will refer to the 2024 Global Initiative for Asthma (GINA).^[6]
60

2.2.2 Types of interventions

All participants with severe asthma received routine therapy with high-dose ICS-LABA combinations. Biologic therapies were administered strictly as add-on treatments to this background regimen. The investigated biologics included anti-IgE treatment (omalizumab), anti-IL-5/5R α treatment (mepolizumab, reslizumab, benralizumab), anti-IL-4R α treatment (dupilumab), and anti-TSLP treatment (tezepelumab).^[6]

2.2.3 Types of comparisons

The control group will be given routine therapy or corresponding placebos.

2.2.4 Types of outcomes

The literature is required to report 1 or more of the following outcomes: annualized asthma exacerbation rate (AER), the change from baseline in oral corticosteroids (OCS) dosage, the change from baseline in pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV₁), asthma control questionnaire (ACQ), asthma control test (ACT), asthma quality of life questionnaire (AQLQ), number of hospitalizations due to asthma, blood eosinophil count, and fractional exhaled nitric oxide (FeNO) levels.

Moreover, we will collect information regarding adverse events and serious adverse events caused by biologic therapy. Thus, we can evaluate the safety of biologics in patients with asthma.

2.2.5 Types of studies

This study will only include eligible SRs/MAs of randomized controlled trials (RCTs) for analysis.

2.3 Exclusion criteria

Studies meeting any of the following criteria will be excluded: (1) Articles for which the full text is not available, (2) Articles without available data, (3) Duplicate or retracted studies, (4) Articles in a

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4 111 language other than English.

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7 112 **2.4 Search strategy**

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9 113 Two authors (QX and BX) will independently carry out the retrieval of literature. PubMed,
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11
12 114 EMBASE, Cochrane Library, Web of Science, and Scopus databases will be searched for literature.
13
14 115 Conference abstracts from the American Thoracic Society International Conference and the
15
16
17 116 European Respiratory Society International Congress will also be searched. The search period will
18
19
20 117 cover from the inception of each database to March 1, 2025. The search terms used include:
21
22 118 “Mepolizumab”, “Reslizumab”, “Benralizumab”, “Omalizumab”, “Dupilumab”, “Tezepelumab”,
23
24
25 119 “Asthma”, “systematic review”, “meta-analysis”, and “indirect treatment comparison”. The search
26
27
28 120 strategy used in PubMed database is listed in **Table 1**. The full search strategy is provided in
29
30 121 **Supplementary File 2**.

31
32
33 122 **Table 1 Search strategy in PubMed**

No	Search terms
#1	((((((((((Mepolizumab[MeSH Terms]) OR (Mepolizumab[Title/Abstract]) OR (SB-240563[Title/Abstract])) OR (SB240563[Title/Abstract])) OR (Nucala[Title/Abstract])) OR (Bosatria[Title/Abstract])) OR ((((((((((Reslizumab[MeSH Terms]) OR (Reslizumab[Title/Abstract]) OR (Cinqair[Title/Abstract])) OR (SCH-55700[Title/Abstract])) OR (SCH 55700[Title/Abstract])) OR (SCH55700[Title/Abstract])) OR (DCP-835[Title/Abstract])) OR (DCP 835[Title/Abstract])) OR (DCP835[Title/Abstract])) OR (CEP-38072[Title/Abstract])) OR (CEP38072[Title/Abstract])) OR (((((Benralizumab[MeSH Terms]) OR (Benralizumab[Title/Abstract]) OR (MEDI-563[Title/Abstract])) OR (MEDI 563[Title/Abstract])) OR (Fasenra[Title/Abstract])) OR (BIW-8405[Title/Abstract])) OR ((Omalizumab[MeSH Terms]) OR (Xolair[Title/Abstract])) OR ((((((Dupilumab[MeSH Terms]) OR (Dupilumab[Title/Abstract]) OR

(SAR231893[Title/Abstract]) OR (SAR-231893[Title/Abstract]) OR (REGN668[Title/Abstract]) OR
 (REGN-668[Title/Abstract]) OR (Dupixent[Title/Abstract]) OR ((((((Tezepelumab[MeSH Terms]) OR
 (Tezepelumab[Title/Abstract]) OR (MEDI-9929[Title/Abstract]) OR (MEDI9929[Title/Abstract]) OR
 (MEDI-19929[Title/Abstract]) OR (AMG-157[Title/Abstract]) OR (tezspire[Title/Abstract]) OR
 (tezepelumab-ekko[Title/Abstract])))
 #2 (((Asthma[MeSH Terms]) OR (Asthmas[Title/Abstract]) OR (Asthma, Bronchial[Title/Abstract]) OR (Bronchial
 Asthma[Title/Abstract]))
 #3 (((((((((((Meta-Analysis as Topic[MeSH Terms]) OR (Meta Analysis[Publication Type])) OR (meta
 analysis[Title/Abstract]) OR (meta analyses[Title/Abstract]) OR (meta-analysis[Title/Abstract]) OR
 (meta-analyses[Title/Abstract]) OR (data pooling[Title/Abstract]) OR (data poolings[Title/Abstract]) OR
 (clinical trial overview[Title/Abstract]) OR (clinical trial overviews[Title/Abstract]) OR (systematic
 review[Title/Abstract]) OR (systematic reviews[Title/Abstract]) OR (indirect treatment comparison
 [Title/Abstract]))
 #4 #1 AND #2 AND #3

2.5 Study selection

After removal of duplicate studies, two reviewers (QX and YH) will individually examine the titles and abstracts of eligible articles that meet the inclusion and exclusion criteria, and exclude irrelevant studies. EndNote 20 software will be used to generate citations and remove duplicate articles.^[11]

Then, two authors (QX and YH) will independently review the full texts of remaining articles and determine the final studies to be included in umbrella review. All disagreements will be resolved by the third independent author (MW). The process of selecting studies is illustrated in **Figure 1**.

To prevent the double-counting of data, we will implement a systematic approach to manage

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2
3
4 131 overlapping primary studies across included SRs/MAs. Initially, we will create a comprehensive
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6
7 132 inventory of all primary studies and identify any overlaps. Then, we will exclude duplicate data to
8
9 133 ensure that data from each primary study are included only once. Additionally, if multiple SRs/MAs
10
11
12 134 include the same primary studies, the datasets may be merged. In the final umbrella review, we will
13
14 135 report the methods used to handle overlapping primary studies.

17 136 **2.6 Data extraction**

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19
20 137 Data extraction will be conducted by two researchers (BX and YH). We will extract information
21
22 138 from eligible SRs/MAs. The extracted information of SRs/MAs includes name of first author, year of
23
24
25 139 publication, title of SRs/MAs, country, database searched, number of clinical studies, sample size per
26
27 140 group, disease duration, average age per group, gender ratio per group, type and dose of biologics,
28
29
30 141 treatment duration, type of comparisons, blood eosinophil count, FeNO, IgE, sIgE levels, efficacy
31
32
33 142 and safety outcomes, type of effect sizes, effect sizes for efficacy and safety outcomes,
34
35 143 heterogeneity, and publication bias. Any discrepancies will be resolved by discussion.

36
37
38 144 To enhance the depth and robustness of our analysis, firstly, we will extract GRADE ratings (e.g.,
39
40 145 high, moderate, low, very low) for critical outcomes from SRs/MAs. Furthermore, we will also
41
42
43 146 collect information on the methodological quality of these SRs/MAs using tools like AMSTAR 2,
44
45
46 147 including the name and version of the assessment tool used, its core evaluation criteria or domains,
47
48 148 assigned scores, and any conclusions drawn regarding the certainty of the evidence.

51 149 **2.7 Quality assessment**

52
53 150 All quality assessments will be conducted by two independent reviewers (QX and YH).
54
55
56 151 Discrepancies will be resolved by consulting a third reviewer (MW). Before the quality assessment
57
58
59 152 process, all reviewers will participate in a training session focused on the use of these quality
60

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3
4 153 assessment tools to enhance inter-rater agreement and minimize bias.

6 7 154 2.7.1 Reporting quality assessment

8
9 155 The reporting quality of the included SRs/MAs will be evaluated using the PRISMA 2020
10
11 statement.^[12] It consists of 27 items and is scored as follows. A complete report is worth 1 point, a
12 156
13 partial report is worth 0.5 points, and an incomplete report is worth 0 points. If all required content is
14 157
15 reported, the item will be classified as "complete report", if $\geq 50\%$ of the reported content is reported
16
17 158
18 with some key information missing, it will be classified as "partial report", if $< 50\%$ of the reported
19
20 159
21 content is reported or critical elements are missing, it will be classified as "incomplete report". The
22 160
23 total score of PRISMA statement is 27 points. In the final evaluation, a score of ≤ 15 indicates that
24
25 161
26 the report has relatively serious information defects, a score of 15.5-21 indicates that the report has
27 162
28 some defects, and a score of 21.5-27 indicates that the report is relatively complete.^[13]

30 163 31 32 164 2.7.2 Risk of bias (Methodological quality) assessment

33
34
35 165 In this umbrella review, we will assess the methodological quality of included SRs/MAs using the
36
37 AMSTAR 2 tool.^[14] It includes 16 items, with 7 key items. The AMSTAR 2's development team
38 166
39 recommended focusing on the methodological conditions of key items and determining the overall
40 167
41 quality. Each item has the following options: yes, partial yes, no. Methodological quality of each
42
43 168
44 SR/MA will be categorized as high, moderate, low and critically low.

45
46 169
47
48 170 Furthermore, we will assess the risk of bias of primary studies through seven aspects: random
49
50 sequence generation (selection bias), allocation concealment (selection bias), blinding of participants
51 171
52 and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete
53 172
54 outcome data (attrition bias), selective reporting (reporting bias) and other bias.^[15] In our final
55
56 173
57 review, we will report these assessments, discussing their potential impact on the overall
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4 175 conclusions.

6 7 176 2.7.3 Quality of evidence assessment

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9 177 In terms of quality of evidence, we will apply the GRADE system to assess.^{[16][17]} It will be classified
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12 178 into four grades: high, moderate, low, and very low. The upgrading factors for evidence quality
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14 179 include large effect size, residual confounding, dose-response relationship, and adequate sample size,
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17 180 while the degrading factors include limitations of the study, inconsistency, indirectness, publication
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20 181 bias, and imprecision.

22 182 **2.8 Management of duplicate reports**

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25 183 To address duplicate publications systematically, we will implement manual verification to identify
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27 184 potential duplicates based on overlapping titles, author affiliations, trial registration numbers, and
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29
30 185 data characteristics. Confirmed duplicates will be resolved by prioritizing the most recent publication
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33 186 to capture methodological updates. If publications are within 6 months of each other, the study with
34
35 187 the larger sample size and more comprehensive data will be selected. All decisions will be reviewed
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38 188 independently by two researchers, with discrepancies resolved through consensus. The entire process
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41 189 will be thoroughly documented to ensure reproducibility.

43 190 **2.9 Statistical analysis**

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46 191 All analyses will be conducted through “meta” package in R 4.3.3 software. Outcomes will be
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48 192 expressed as mean difference (MD) and risk ratio (RR) with corresponding 95% confidence intervals
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51 193 (CIs). Firstly, we will assess the heterogeneity of included studies by using the Cochran’s Q test and
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53 194 I^2 statistics.^[18] $P < 0.1$ or $I^2 > 40\%$ indicates significant heterogeneity, and the random-effects model
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56 195 will be used.^[19] Or else, we will choose the fixed-effects model. Then, we will calculate pooled MDs
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59 196 or RRs with 95% CIs for each outcome of different biologics. The results will be presented in text,
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4 197 tables, and figures. $P < 0.05$ indicates statistical significance.
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7 198 In addition, subgroup analysis will be conducted to explore the potential sources of heterogeneity.
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9 199 The subgroups will include population characteristics (age, baseline disease severity, and blood
10
11 eosinophil count) and intervention variables (types of biologics, dosage, and treatment duration). The
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14 201 publication bias will be evaluated through the funnel plot and the Egger's test, which will only be
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17 202 performed when the number of studies exceeds 10 to ensure sufficient statistical power.
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19 203 **3 DISCUSSION**

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22 204 In recent years, many SRs/MAs have been published. However, concerns have been raised as the
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25 205 generalizability and validity of such analyses. Different study populations and types of original
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27 206 studies, combined with varying degrees of methodological flaws in SRs/MAs, may lead to
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30 207 misleading clinical decisions. Employing the latest evidence-based medicine analysis, the umbrella
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33 208 review based on SRs/MAs provides more robust and reliable evidence for clinical practice and
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35 209 partially compensates for the limitations of individual SRs/MAs. [20]
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38 210 Asthma is a serious global health problem, and people with severe asthma have more severe
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40 211 symptoms, frequent exacerbations, and significant medical economic burden.[21] In previous
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43 212 SRs/MAs, biologics have demonstrated promising efficacy and safety,[22][23][24] and are considered a
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46 213 promising treatment for severe asthma. Nevertheless, the overall quality of these SRs/MAs is still
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48 214 unclear, promoting the need for an umbrella review. The findings of this review will further
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51 215 strengthen the evidence-based medical basis for the application of biologics in severe asthma and
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53 216 provide guidance for clinical practice.
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56 217 Sample size is a critical factor influencing the reliability of SRs/MAs. Adequate sample size
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59 218 enhances the precision of effect estimates and reduces the risk of bias, both of which are essential for
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4 219 high-quality evidence. Therefore, incorporating sample size as an additional factor in the GRADE
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7 220 system can provide a more comprehensive evaluation of the evidence quality. In this study, we will
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9 221 pay special attention to the sample size of included SRs/MAs to ensure the robustness of our
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12 222 findings.

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14 223 However, this study has some limitations. Firstly, only articles in English will be included in this
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17 224 study, and important studies published in other languages may be excluded. As most databases and
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20 225 literature resources are in English, language restrictions ensure data accuracy and consistency, which
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22 226 facilitates precise data extraction and analysis. Secondly, some subjective factors may affect the
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25 227 evaluation of literature quality.

26 27 228 **PATIENT AND PUBLIC INVOLVEMENT**

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30 229 Patients and public will not participate in the design and implementation of the study. The research
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33 230 results will be made available to the patient and public.

34 35 231 **ETHICS AND DISSEMINATION**

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38 232 Since this study will use publicly available data, ethics approval is not required. We will disseminate
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40
41 233 the results of this review through a peer-reviewed journal.

42 43 234 **Author affiliations**

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45 235 ¹National Regional Medical Center of TCM (Pulmonary Disease), the First Affiliated Hospital of
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48 236 Henan University of Chinese Medicine, Zhengzhou, Henan, China.

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51 237 ²The First Clinical Medical School, Henan University of Chinese Medicine, Zhengzhou, Henan,
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53 238 China.

54 55 56 239 **Author contributions**

57
58
59 240 QX designed the study, submitted the registration to PROSPERO, and wrote the manuscript. QX and
60

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4 241 BX completed the search strategy. QX and YH revised the language. MW is responsible for directing
5
6
7 242 the overall study. All authors approved the manuscript.
8

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10
11
12 244 This work was supported by National Key Research and Development Program of China
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15
16
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18
19
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21
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23
24
25 249 Henan Province (232102310472).
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27 250 **Competing interests**

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29
30 251 None declared.
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32 252 **Patient and public involvement**

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35 253 Patients and the public will not involve in the design, or implementation, or report, or dissemination
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38 254 plans of this review.
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40 255 **Patient consent for publication**

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43 256 Not applicable.
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45 257 **Provenance and peer review**

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47
48 258 Not commissioned; externally peer reviewed.
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50 259 **Data availability statement**

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53 260 After completing the study, data are available from corresponding author.
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56 261 **Supplemental material**

57
58
59 262 The details of the PRISMA-P 2015 checklist and the search strategy can be viewed in Supplemental
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material.

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Figure Legends

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329 Figure 1 Flow chart diagram of study selection.

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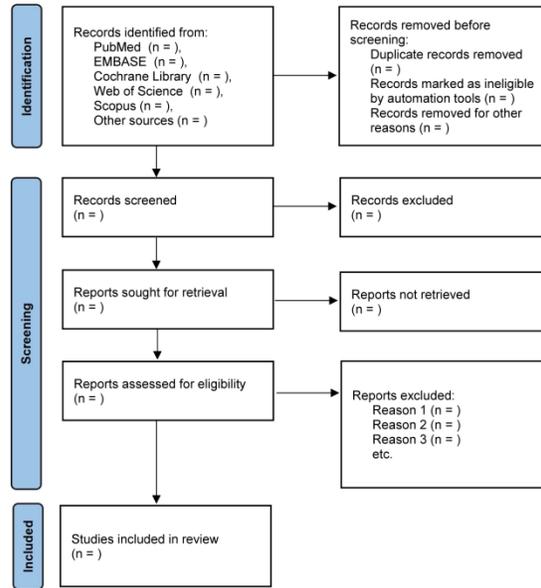


Figure 1 Flow chart diagram of study selection.

210x297mm (300 x 300 DPI)

Supplementary file 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 Checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12-13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits such that it could be repeated	6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), pre-planned data assumptions and simplifications	4-5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kendall's)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Supplementary file 2. The details of the search strategy.

Pubmed
<p>((((((((Mepolizumab[MeSH Terms]) OR (SB-240563[Title/Abstract])) OR (SB240563[Title/Abstract])) OR (Nucala[Title/Abstract])) OR (Bosatria[Title/Abstract])) OR</p>
<p>((((((((Reslizumab[MeSH Terms]) OR (Cinqair[Title/Abstract])) OR (SCH-55700[Title/Abstract])) OR (SCH 55700[Title/Abstract])) OR (SCH55700[Title/Abstract])) OR (DCP-835[Title/Abstract])) OR (DCP 835[Title/Abstract])) OR (DCP835[Title/Abstract])) OR (CEP-38072[Title/Abstract])) OR (CEP38072[Title/Abstract])) OR</p>
<p>(((Benralizumab[MeSH Terms]) OR (MEDI-563[Title/Abstract])) OR (MEDI 563[Title/Abstract])) OR (Fasenra[Title/Abstract])) OR (BIW-8405[Title/Abstract])) OR</p>
<p>((Omalizumab[MeSH Terms]) OR (Xolair[Title/Abstract])) OR</p>
<p>((((((Dupilumab[MeSH Terms]) OR (SAR231893[Title/Abstract])) OR (SAR-231893[Title/Abstract])) OR (REGN668[Title/Abstract])) OR (REGN-668[Title/Abstract])) OR (Dupixent[Title/Abstract])) OR</p>
<p>((((((Tezepelumab[MeSH Terms]) OR (MEDI-9929[Title/Abstract])) OR (MEDI9929[Title/Abstract])) OR (MEDI-19929[Title/Abstract])) OR (AMG-157[Title/Abstract])) OR (tezspire[Title/Abstract])) OR (tezepelumab-ekko[Title/Abstract])) AND</p>
<p>(((Asthma[MeSH Terms]) OR (Asthmas[Title/Abstract])) OR (Asthma, Bronchial[Title/Abstract])) OR (Bronchial Asthma[Title/Abstract])) AND</p>
<p>((((((((((((Meta-Analysis as Topic[MeSH Terms]) OR (Meta Analysis[Publication Type])) OR (meta analysis[Title/Abstract])) OR (meta analyses[Title/Abstract])) OR (meta-analysis[Title/Abstract])) OR (meta-analyses[Title/Abstract])) OR (data pooling[Title/Abstract])) OR (data poolings[Title/Abstract])) OR (clinical trial overview[Title/Abstract])) OR (clinical trial overviews[Title/Abstract])) OR</p>

Supplementary Material

(systematic review[Title/Abstract])) OR (systematic reviews[Title/Abstract]))
OR (indirect treatment comparison [Title/Abstract]))

Embase

#1 'asthma'/exp

#2 'asthma'

#3 'asthma bronchiale' OR 'asthma pulmonale' OR 'asthma, bronchial' OR
'asthmatic' OR 'asthmatic subject' OR 'bronchial asthma' OR 'bronchus asthma' OR
'chronic asthma' OR 'lung allergy'

#4 #1 OR #2 OR #3

#5 'mepolizumab'/exp

#6 'mepolizumab'

#7 'bat 2606' OR 'bat2606' OR 'bosatria' OR 'nucala' OR 'sb 240563' OR 'sb-
240563' OR 'sb240563'

#8 'reslizumab'/exp

#9 'reslizumab'

#10 'cep 38072' OR 'cep38072' OR 'cinquaero' OR 'cinqair' OR 'dcp 835' OR
'dcp835' OR 'sch 55700' OR 'sch55700'

#11 'benralizumab'/exp

#12 'benralizumab'

#13 'biw 8405' OR 'biw8405' OR 'fasentra' OR 'khk 4563' OR 'khk4563' OR 'medi
563' OR 'medi563'

#14 'omalizumab'/exp

#15 'omalizumab'

#16 'aomaishu' OR 'cmab 007' OR 'cmab007' OR 'fb 317' OR 'fb317' OR 'gbr 310' OR 'gbr310' OR 'genolair' OR 'gnr 044' OR 'gnr044' OR 'hu 901' OR 'hu901' OR 'monoclonal antibody E 25' OR 'monoclonal antibody E25' OR 'olizumab' OR 'omalizumab alfa' OR 'omalizumab alpha' OR 'omlyclo' OR 'rg 3648' OR 'rg3648' OR 'rhumab 25' OR 'rhumab e25' OR 'sti 004' OR 'sti004' OR 'syn 008' OR 'syn008' OR 'tev 45779' OR 'tev45779' OR 'xolair'

#17 'dupilumab'/exp

#18 'dupilumab'

#19 'bat 2406' OR 'bat2406' OR 'dupixent' OR 'regn 668' OR 'regn668' OR 'sar 231893' OR 'sar231893'

#20 'tezepelumab'/exp

#21 'tezepelumab'

#22 'amg 157' OR 'amg157' OR 'medi 9929' OR 'medi9929' OR 'tezepelumab ekko' OR 'tezepelumab-ekko' OR 'tezspire'

#23 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22

#24 #4 AND #23

Cochrane Library

#1 MeSH descriptor: [Mepolizumab] explode all trees

#2 MeSH descriptor: [Reslizumab] explode all trees

#3 MeSH descriptor: [Benralizumab] explode all trees

#4 MeSH descriptor: [Omalizumab] explode all trees

#5 Xolair

#6 MeSH descriptor: [Dupilumab] explode all trees

Supplementary Material

#7	MeSH descriptor: [Tezepelumab] explode all trees
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	MeSH descriptor: [Asthma] explode all trees
#10	Asthma, Bronchial
#11	Asthmas
#12	Bronchial Asthma
#13	#9 OR #10 OR #11 OR #12
#14	#8 AND #13
Web of Science	
TS = (Mepolizumab OR Reslizumab OR Benralizumab OR Omalizumab OR Dupilumab OR Tezepelumab) AND TS = (Asthma)	
Scopus	
(TITLE-ABS-KEY (asthma)) AND ((TITLE-ABS-KEY (mepolizumab) OR TITLE-ABS-KEY (reslizumab) OR TITLE-ABS-KEY (benralizumab) OR TITLE-ABS-KEY (omalizumab) OR TITLE-ABS-KEY (dupilumab) OR TITLE-ABS-KEY (tezepelumab)))	

BMJ Open

The effectiveness of biologics for patients with severe asthma: study protocol for an umbrella review of systematic reviews and meta-analyses

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2024-096874.R2
Article Type:	Protocol
Date Submitted by the Author:	24-Mar-2025
Complete List of Authors:	Xiao, Qionghua; The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, National Regional Medical Center of TCM (Pulmonary Disease); Henan University of Chinese Medicine, The First Clinical Medical School Xue, Bingyu; The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, National Regional Medical Center of TCM (Pulmonary Disease); Henan University of Chinese Medicine, The First Clinical Medical School Huang, Yuanming; The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, National Regional Medical Center of TCM (Pulmonary Disease); Henan University of Chinese Medicine, The First Clinical Medical School Wang, Minghang; The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, National Regional Medical Center of TCM (Pulmonary Disease)
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Respiratory medicine
Keywords:	Asthma < THORACIC MEDICINE, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, RESPIRATORY MEDICINE (see Thoracic Medicine)

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Manuscripts

The effectiveness of biologics for patients with severe asthma: study protocol for an umbrella review of systematic reviews and meta-analyses

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Word count: 2510.

ABSTRACT

Introduction: Many systematic reviews and meta-analyses (SRs/MAs) have evaluated the efficacy of biologic therapies for severe asthma. However, the overall quality of these SRs/MAs is unclear, which may influence the selection of biologics and lead to misleading clinical decisions. This umbrella review aims to objectively evaluate the overall quality of these SRs/MAs and reassess the efficacy of biologic therapies for severe asthma. Thus, this study will provide reliable evidence for clinical practice.

Methods and analysis: A systematic search will be performed in PubMed, Embase, Cochrane Library, Web of Science, Scopus, and conference abstracts up to March 1, 2025. Literature screening and data extraction will be conducted according to predefined inclusion and exclusion criteria. We

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4 23 will evaluate the reporting quality, methodological quality, and evidence quality of these SRs/MAs
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6 24 using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020
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9 25 statement, PRISMA for Network Meta-Analysis (PRISMA-NMA) 2015 checklist, A MeaSurement
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12 26 Tool to Assess Systematic Reviews (AMSTAR) 2, Cochrane Risk of Bias 1.0 (RoB 1.0), and
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14 27 Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.
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17 28 Additionally, the re-analysis of outcomes will be performed using R software (version 4.3.3).

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20 29 **Ethics and dissemination:** Since this umbrella review will use publicly available data, ethics
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22 30 approval is not required. The results of this study will be disseminated through publication in a
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25 31 peer-reviewed journal.

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27 32 **PROSPERO registration number:** CRD42024607393.

28
29
30 33 **Keywords:** biologics, severe asthma, umbrella review, protocol

31 32 34 **Article Summary**

33 34 35 **Strengths and limitations of this study**

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37 36 (1) This study is the first umbrella review that evaluates the efficacy of biologic therapies for patients
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40 37 with severe asthma.

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43 38 (2) This umbrella review will objectively evaluate the overall quality of eligible SRs/MAs.

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46 39 (3) Only articles in English will be included in this study, which may result in the exclusion of
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48 40 potentially relevant studies published in other languages.

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51 41 (4) Potential subjective bias may influence the evaluation of literature quality.

52 53 42 **1 INTRODUCTION**

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56 43 Asthma is a prevalent chronic respiratory disease characterized by airway inflammation and airway
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59 44 hyperresponsiveness. It often presents with recurrent wheezing, shortness of breath, chest tightness,
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4 45 cough, and other symptoms.^[1] Asthma is a serious global health problem, affecting about 300 million
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7 46 people worldwide and causing about 250,000 deaths annually.^[2] Additionally, and more importantly,
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10 47 patients with severe asthma have more significant symptoms, more frequent exacerbations, and more
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12 48 serious adverse effects of medications, which can interfere with patients' daily lives, sleep, and
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14 49 physical activity.^[3] A Dutch study reported that about 3.7% of people with asthma suffer from severe
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17 50 asthma.^[4] Furthermore, severe asthma is associated with higher healthcare expenditures. A Canadian
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20 51 study demonstrated that severe asthma accounts for over 60% of total asthma-related costs.^[5]

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22 52 Severe asthma refers to patients who remain uncontrolled despite adhering to maximal optimized
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25 53 high-dose inhaled corticosteroids (ICS)/long-acting beta-agonists (LABA) treatment and
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27 54 management of associated factors, or who worsen when high-dose treatment is decreased.^[6] For
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30 55 these patients, add-on therapies, mainly emerging biologics, are needed to provide new hope for the
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33 56 treatment of severe asthma. Biologics can modulate the immuno-inflammatory cascade in the
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35 57 pathological course of severe asthma by precisely targeting inflammatory cytokines.^[6] Biologics for
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38 58 severe asthma mainly include anti-immunoglobulin E (anti-IgE) treatment (e.g., omalizumab),
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40 59 anti-interleukin-5/5R α (anti-IL-5/5R α) treatment (e.g., mepolizumab, reslizumab, benralizumab),
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43 60 anti-interleukin-4R α (anti-IL-4R α) treatment (e.g., dupilumab), and anti-thymic stromal
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46 61 lymphopoietin (anti-TSLP) treatment (e.g., tezepelumab). In previous studies, biologics have been
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48 62 shown to be beneficial for severe asthma, as they can reduce the frequency of acute exacerbations
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51 63 and hospitalizations, improve lung function and quality of life, and decrease reliance on systemic
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53 64 corticosteroids.^{[7][8][9]}

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56 65 Recently, numerous systematic reviews and meta-analyses (SRs/MAs) have demonstrated the
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59 66 efficacy of biologics for severe asthma. However, these SRs/MAs also highlighted potential
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4 67 limitations. The reliability of the results may be affected by the heterogeneity among studies and
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7 68 other risks of bias. The methodological, reporting, and evidence quality of these SRs/MAs remain
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10 69 unclear. The umbrella review can evaluate the overall quality of relevant SRs/MAs in detail, thereby
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12 70 providing high-quality evidence for clinical practice. To date, no umbrella reviews have been
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15 71 published on this topic, underscoring the need for this study to synthesize existing evidence.

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17 72 In this umbrella review, the reporting, methodological, and evidence quality of relevant SRs/MAs
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20 73 will be evaluated using Preferred Reporting Items for Systematic Reviews and Meta-Analyses
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22 74 (PRISMA) 2020 statement, PRISMA for Network Meta-Analysis (PRISMA-NMA) 2015 checklist,
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25 75 A MeaSurement Tool to Assess Systematic Reviews (AMSTAR) 2, Cochrane Risk of Bias 1.0 (RoB
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27 76 1.0), and Grading of Recommendations Assessment, Development, and Evaluation (GRADE)
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30 77 system. Additionally, we will re-evaluate the efficacy of biologics for patients with severe asthma.
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33 78 Ultimately, this study aims to provide evidence-based medical analysis for the use of biologics in
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35 79 severe asthma.

36 37 38 80 **2 METHODS AND ANALYSIS**

39 40 81 **2.1 Design and registration**

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43 82 This protocol was registered in PROSPERO (Registration number: CRD42024607393). The initial
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46 83 version was registered on October 29, 2024. It will be reported according to Preferred Reporting
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48 84 Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) 2015 statement.^[10] The
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51 85 detailed PRISMA-P 2015 checklist can be found in **Supplementary file 1**. This study commenced
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53 86 on November 15, 2024, and is expected to be completed by May 31, 2025.

54 55 56 87 **2.2 Inclusion criteria**

57 58 88 **2.2.1 Types of participants**

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4 89 This umbrella review will consider SRs/MAs that focus on participants aged ≥ 12 years with severe
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6 90 asthma. While the PROSPERO registration included participants aged ≥ 6 years, the final analysis
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9 91 will be restricted to ≥ 12 years due to insufficient high-quality evidence in younger populations. This
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12 92 adjustment ensures consistency with clinical practice and avoids bias from limited data. The criteria
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14 93 for severe asthma will refer to the 2024 Global Initiative for Asthma (GINA).^[6]

17 94 2.2.2 Types of interventions

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19 95 All participants with severe asthma received routine therapy with high-dose ICS-LABA
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22 96 combinations. Biologic therapies were administered strictly as add-on treatments to this background
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25 97 regimen. The investigated biologics included anti-IgE treatment (omalizumab), anti-IL-5/5R α
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27 98 treatment (mepolizumab, reslizumab, benralizumab), anti-IL-4R α treatment (dupilumab), and
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30 99 anti-TSLP treatment (tezepelumab).^[6]

32 100 2.2.3 Types of comparisons

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35 101 The control group will be given routine therapy or corresponding placebos.

37 102 2.2.4 Types of outcomes

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40 103 The literature is required to report 1 or more of the following outcomes: annualized asthma
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43 104 exacerbation rate (AER), the change from baseline in oral corticosteroids (OCS) dosage, the change
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46 105 from baseline in pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV1), asthma
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48 106 control questionnaire (ACQ), asthma control test (ACT), asthma quality of life questionnaire
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51 107 (AQLQ), number of hospitalizations due to asthma, blood eosinophil count, and fractional exhaled
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53 108 nitric oxide (FeNO) levels.

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56 109 Moreover, we will collect information regarding adverse events and serious adverse events caused
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59 110 by biologic therapy. Thus, we can evaluate the safety of biologics in patients with asthma.

2.2.5 Types of studies

This study will include eligible SRs/MAs of randomized controlled trials (RCTs) for analysis. Notably, we will also include articles on indirect treatment comparisons (ITCs) in our umbrella review, such as network meta-analyses (NMAs).

2.3 Exclusion criteria

Studies meeting any of the following criteria will be excluded: (1) Articles for which the full text is not available, (2) Articles without available data, (3) Duplicate or retracted studies, (4) Articles in a language other than English.

2.4 Search strategy

Two authors (QX and BX) will independently carry out the retrieval of literature. PubMed, Embase, Cochrane Library, Web of Science, and Scopus databases will be searched for literature. Conference abstracts from the American Thoracic Society International Conference, the European Respiratory Society International Congress, the CHEST Annual Meeting (American College of Chest Physicians), and the Asia Pacific Society of Respiratory Congress will also be searched. The search will cover the period from the inception of each database to March 1, 2025. The search terms used include: “Mepolizumab”, “Reslizumab”, “Benralizumab”, “Omalizumab”, “Dupilumab”, “Tezepelumab”, “Asthma”, “systematic review”, “meta-analysis”, and “indirect treatment comparison”. The search strategy used in the PubMed database is listed in **Table 1**. The full search strategy is provided in **Supplementary file 2**.

Table 1 Search strategy in PubMed

No	Search terms
#1	((((((((((Mepolizumab[MeSH Terms]) OR (Mepolizumab[Title/Abstract]) OR (SB-240563[Title/Abstract])) OR

(SB240563[Title/Abstract])) OR (Nucala[Title/Abstract])) OR (Bosatria[Title/Abstract])) OR
 (((((((Reslizumab[MeSH Terms]) OR (Reslizumab[Title/Abstract]) OR (Cinqair[Title/Abstract])) OR
 (SCH-55700[Title/Abstract])) OR (SCH 55700[Title/Abstract])) OR (SCH55700[Title/Abstract])) OR
 (DCP-835[Title/Abstract])) OR (DCP 835[Title/Abstract])) OR (DCP835[Title/Abstract])) OR
 (CEP-38072[Title/Abstract])) OR (CEP38072[Title/Abstract])) OR (((Benralizumab[MeSH Terms]) OR
 (Benralizumab[Title/Abstract]) OR (MEDI-563[Title/Abstract])) OR (MEDI 563[Title/Abstract])) OR
 (Fasenra[Title/Abstract])) OR (BIW-8405[Title/Abstract])) OR ((Omalizumab[MeSH Terms]) OR
 (Xolair[Title/Abstract])) OR (((Dupilumab[MeSH Terms]) OR (Dupilumab[Title/Abstract]) OR
 (SAR231893[Title/Abstract])) OR (SAR-231893[Title/Abstract])) OR (REGN668[Title/Abstract])) OR
 (REGN-668[Title/Abstract])) OR (Dupixent[Title/Abstract])) OR (((Tezepelumab[MeSH Terms]) OR
 (Tezepelumab[Title/Abstract]) OR (MEDI-9929[Title/Abstract])) OR (MEDI9929[Title/Abstract])) OR
 (MEDI-19929[Title/Abstract])) OR (AMG-157[Title/Abstract])) OR (tezspire[Title/Abstract])) OR
 (tezepelumab-ekko[Title/Abstract]))

#2 (((Asthma[MeSH Terms]) OR (Asthmas[Title/Abstract])) OR (Asthma, Bronchial[Title/Abstract])) OR (Bronchial
 Asthma[Title/Abstract]))

#3 (((((((((((Meta-Analysis as Topic[MeSH Terms]) OR (Meta Analysis[Publication Type])) OR (meta
 analysis[Title/Abstract])) OR (meta analyses[Title/Abstract])) OR (meta-analysis[Title/Abstract])) OR
 (meta-analyses[Title/Abstract])) OR (data pooling[Title/Abstract])) OR (data poolings[Title/Abstract])) OR
 (clinical trial overview[Title/Abstract])) OR (clinical trial overviews[Title/Abstract])) OR (systematic
 review[Title/Abstract])) OR (systematic reviews[Title/Abstract])) OR (indirect treatment comparison
 [Title/Abstract]))

#4 #1 AND #2 AND #3

2.5 Study selection

After removal of duplicate studies, two reviewers (QX and YH) will individually examine the titles and abstracts of eligible articles that meet the inclusion and exclusion criteria, and exclude irrelevant studies. EndNote (version 20) software will be used to generate citations and remove duplicate articles.^[11] Then, two authors (QX and YH) will independently review the full texts of remaining articles and determine the final studies to be included in the umbrella review. All disagreements will be resolved by the third independent author (MW). The process of selecting studies is illustrated in

Figure 1.

To prevent the double counting of data, we will implement a systematic approach to manage overlapping primary studies across included SRs/MAs. Initially, we will create a comprehensive inventory of all primary studies and identify any overlaps. Then, we will exclude duplicate data to ensure that data from each primary study are included only once. Additionally, if multiple SRs/MAs include the same primary studies, the datasets may be merged. In the final umbrella review, we will report the methods used to handle overlapping primary studies.

2.6 Data extraction

Data extraction will be conducted by two researchers (BX and YH). We will extract information from eligible SRs/MAs. Extracted information from each SR/MA includes name of first author, year of publication, title of SR/MA, country, databases searched, number of clinical studies, sample sizes per group, disease duration, average age per group, gender ratio per group, type and dose of biologics, treatment duration, type of comparisons, blood eosinophil count, FeNO, IgE, sIgE levels, efficacy and safety outcomes, type of effect sizes, effect sizes for efficacy and safety outcomes, heterogeneity, and publication bias. Any discrepancies will be resolved by discussion.

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4 153 To enhance the depth and robustness of our analysis, firstly, we will extract GRADE ratings (e.g.,
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7 154 high, moderate, low, or very low) for critical outcomes from SRs/MAs. Furthermore, we will also
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9 155 collect information on the methodological quality of these SRs/MAs using tools like AMSTAR 2,
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12 156 including the name and version of the assessment tool used, its core evaluation criteria or domains,
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15 157 assigned scores, and any conclusions drawn regarding the certainty of the evidence.
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17 158 **2.7 Quality assessment**

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20 159 All quality assessments will be conducted by two independent reviewers (QX and YH).
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22 160 Discrepancies will be resolved by consulting a third reviewer (MW). Before the quality assessment
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25 161 process, all reviewers will participate in a training session focused on the use of these quality
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27 162 assessment tools to enhance inter-rater agreement and minimize bias.
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30 163 **2.7.1 Reporting quality assessment**

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33 164 The reporting quality of the included SRs/MAs will be evaluated using the PRISMA 2020
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35 165 statement.^[12] It consists of 27 items and is scored as follows: a complete report is worth 1 point, a
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38 166 partial report is worth 0.5 points, and an incomplete report is worth 0 points. If all required content is
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40 167 reported, the item will be classified as “complete report”; if $\geq 50\%$ of the reported content is reported
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43 168 with some key information missing, it will be classified as “partial report”; if $< 50\%$ of the reported
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46 169 content is reported or critical elements are missing, it will be classified as “incomplete report”. The
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48 170 total score of PRISMA statement is 27 points. In the final evaluation, a score of ≤ 15 indicates that
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51 171 the report has relatively serious information defects, a score of 15.5-21 indicates that the report has
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54 172 some defects, and a score of 21.5-27 indicates that the report is relatively complete.^[13]
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56 173 Additionally, the PRISMA-NMA 2015 checklist will be used to assess the reporting quality of the
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59 174 included ITCs.^[14] It includes 32 items, and the total score is 32 points. Scoring follows the same
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4 175 criteria as the PRISMA 2020 statement. In the final evaluation, a score of ≤ 18 indicates that the
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7 176 report has relatively serious information defects, a score of 18.5-25 indicates that the report has some
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9 177 defects, and a score of 25.5-32 indicates that the report is relatively complete.

12 178 2.7.2 Risk of bias (Methodological quality) assessment

14 179 In this umbrella review, we will assess the methodological quality of included SRs/MAs using the
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17 180 AMSTAR 2 tool.^[15] It includes 16 items, with 7 key items. The AMSTAR 2 development team
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20 181 recommended focusing on the methodological conditions of key items and determining the overall
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22 182 quality. Each item has the following options: yes, partial yes, or no. The methodological quality of
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25 183 each SR/MA will be categorized as high, moderate, low, or critically low.

27 184 The methodological quality of ITCs will be assessed using the AMSTAR 2 tool, augmented with
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30 185 NMA-specific criteria from the International Society for Pharmacoeconomics and Outcomes
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33 186 Research, Academy of Managed Care Pharmacy, National Pharmaceutical Council
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35 187 (ISPOR-AMCP-NPC) checklist.^[16] The four criteria include transitivity assessment, direct and
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38 188 indirect evidence consistency, model selection justification, and cautious interpretation of rankings.

40 189 Each item is rated yes, partial yes, or no, with overall quality categorized as high, moderate, low, or
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43 190 critically low.

45 191 Furthermore, we will assess the risk of bias of primary studies through seven aspects: random
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48 192 sequence generation (selection bias), allocation concealment (selection bias), blinding of participants
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51 193 and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete
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53 194 outcome data (attrition bias), selective reporting (reporting bias) and other bias.^[17] In our final
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56 195 review, we will report these assessments, discussing their potential impact on the overall
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59 196 conclusions.

2.7.3 Quality of evidence assessment

In terms of quality of evidence, we will apply the GRADE system to assess it.^{[18][19]} It will be classified into four grades: high, moderate, low, and very low. The upgrading factors for evidence quality include large effect size, residual confounding, dose-response relationship, and adequate sample size, while the degrading factors include study limitations, inconsistency, indirectness, publication bias, and imprecision.

2.8 Management of duplicate reports

To systematically address duplicate publications, we will implement manual verification to identify potential duplicates based on overlapping titles, author affiliations, trial registration numbers, and data characteristics. Confirmed duplicates will be resolved by prioritizing the most recent publication to capture methodological updates. If publications are within 6 months of each other, the study with the larger sample size and more comprehensive data will be selected. All decisions will be reviewed independently by two researchers, and discrepancies will be resolved through consensus. The entire process will be thoroughly documented to ensure reproducibility.

2.9 Statistical analysis

All analyses will be conducted through “meta” package in R 4.3.3 software. Outcomes will be expressed as mean difference (MD) and risk ratio (RR) with corresponding 95% confidence intervals (CIs). Firstly, we will assess the heterogeneity of included studies by using the Cochran’s Q test and I^2 statistics.^[20] $P < 0.1$ or $I^2 > 40\%$ indicates significant heterogeneity, and the random-effects model will be used.^[21] Otherwise, we will choose the fixed-effects model. Then, we will calculate pooled MDs or RRs with 95% CIs for each outcome of different biologics. The results will be presented in the text, tables, and figures. $P < 0.05$ indicates statistical significance.

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4 219 Data from ITC and direct comparison articles will be analyzed together. Sensitivity analysis will also
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7 220 be conducted to evaluate the impact of each study on overall results. When interpreting the results,
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9 221 evidence from both ITC and direct comparison articles will be considered to provide a more
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12 222 comprehensive efficacy assessment. Due to the uncertainty of ITC results, we will interpret the
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14 223 findings cautiously.

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17 224 In addition, subgroup analysis will be conducted to explore the potential sources of heterogeneity.
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20 225 The subgroups will include population characteristics (age, baseline disease severity, and blood
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22 226 eosinophil count) and intervention variables (types of biologics, dosage, and treatment duration). The
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25 227 publication bias will be evaluated through funnel plots and Egger's test, which will only be
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27 228 performed when the number of studies exceeds 10 to ensure sufficient statistical power.

30 229 **3 DISCUSSION**

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33 230 In recent years, many SRs/MAs have been published. However, concerns have been raised about the
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35 231 generalizability and validity of such analyses. Different study populations and types of original
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38 232 studies, combined with varying degrees of methodological flaws in SRs/MAs, may lead to
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40 233 misleading clinical decisions. Employing the latest evidence-based medicine analysis, the umbrella
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43 234 review based on SRs/MAs provides more robust and reliable evidence for clinical practice and
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45 235 compensates for the limitations of individual SRs/MAs.^[22]

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48 236 Asthma is a serious global health problem, and people with severe asthma have more severe
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51 237 symptoms, frequent exacerbations, and significant medical economic burden.^[23] In previous
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53 238 SRs/MAs, biologics have demonstrated promising efficacy and safety, and are considered a
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56 239 promising treatment for severe asthma.^{[24][26]} Nevertheless, the overall quality of these SRs/MAs is
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59 240 still unclear, prompting the need for an umbrella review. The findings of this review will further
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4 241 strengthen the evidence-based medical basis for the application of biologics in severe asthma and
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7 242 provide guidance for clinical practice.
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9 243 Sample size is a critical factor influencing the reliability of SRs/MAs. Adequate sample size
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12 244 enhances the precision of effect estimates and reduces the risk of bias, both of which are essential for
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14 245 high-quality evidence. Therefore, incorporating sample size as an additional factor in the GRADE
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17 246 system can provide a more comprehensive evaluation of the quality of evidence. In this study, we
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20 247 will pay special attention to the sample size of included SRs/MAs to ensure the robustness of our
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22 248 findings.
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25 249 However, this study has some limitations. Firstly, we will include only articles in English and
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27 250 exclude studies published in other languages. As most databases and literature resources are in
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30 251 English, language restrictions help ensure data accuracy and consistency, thereby facilitating precise
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33 252 data extraction and analysis. Secondly, some subjective factors may affect the evaluation of literature
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35 253 quality.
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37 38 254 **PATIENT AND PUBLIC INVOLVEMENT**

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40 255 Patients and public will not participate in the design and implementation of the study. The research
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43 256 results will be made available to the patient and public.
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45 46 257 **ETHICS AND DISSEMINATION**

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48 258 Since this study will use publicly available data, ethics approval is not required. We will disseminate
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51 259 the results of this review through a peer-reviewed journal.
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4 263 ²The First Clinical Medical School, Henan University of Chinese Medicine, Zhengzhou, Henan,
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7 264 China.

9 265 **Author contributions**

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12 266 Qionghua Xiao designed the study, submitted the registration to PROSPERO, and wrote the
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15 267 manuscript. Qionghua Xiao and Bingyu Xue completed the search strategy. Qionghua Xiao and
16
17 268 Yuanming Huang revised the language. Minghang Wang is responsible for directing the overall
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19
20 269 study. Minghang Wang is the guarantor.

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38 276 (232102310472).

39 40 277 **Competing interests**

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43 278 None declared.

44 45 279 **Patient and public involvement**

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48 280 Patients and the public will not involve in the design, or implementation, or report, or dissemination
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51 281 plans of this review.

52 53 282 **Patient consent for publication**

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56 283 Not applicable.

57 58 284 **Provenance and peer review**

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4 285 Not commissioned; externally peer reviewed.
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7 286 **Data availability statement**
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9 287 After completing the study, data are available from corresponding author.
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12 288 **Supplemental material**
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14 289 The details of the PRISMA-P 2015 checklist and the search strategy can be viewed in Supplemental
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17 290 material.
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33 362 **Figure Legends**

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35 363 Figure 1 Flow chart diagram of study selection.

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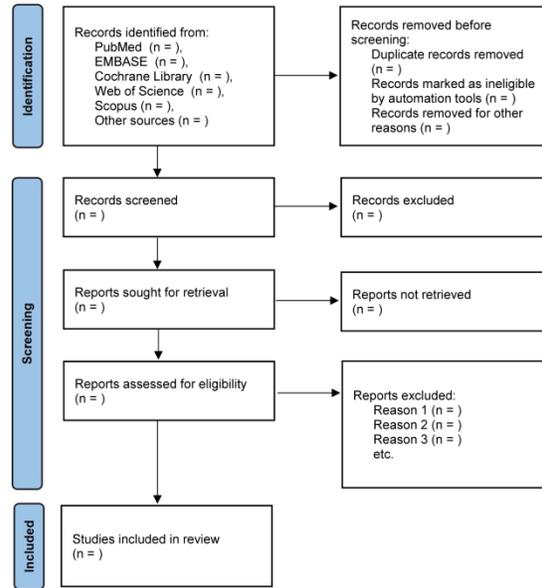


Figure 1 Flow chart diagram of study selection.

210x297mm (300 x 300 DPI)

Supplementary file 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 Checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	12-13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	2-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits such that it could be repeated	6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), pre-planned data assumptions and simplifications	4-5
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kendall's τ)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	-
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary file 2. The details of the search strategy.

Pubmed
<p> ((((((((Mepolizumab[MeSH Terms]) OR (SB-240563[Title/Abstract])) OR (SB240563[Title/Abstract])) OR (Nucala[Title/Abstract])) OR (Bosatria[Title/Abstract])) OR ((((((((Reslizumab[MeSH Terms]) OR (Cinqair[Title/Abstract])) OR (SCH- 55700[Title/Abstract])) OR (SCH 55700[Title/Abstract])) OR (SCH55700[Title/Abstract])) OR (DCP-835[Title/Abstract])) OR (DCP 835[Title/Abstract])) OR (DCP835[Title/Abstract])) OR (CEP- 38072[Title/Abstract])) OR (CEP38072[Title/Abstract])))) OR ((((Benralizumab[MeSH Terms]) OR (MEDI-563[Title/Abstract])) OR (MEDI 563[Title/Abstract])) OR (Fasenra[Title/Abstract])) OR (BIW- 8405[Title/Abstract])))) OR ((Omalizumab[MeSH Terms]) OR (Xolair[Title/Abstract])))) OR ((((((Dupilumab[MeSH Terms]) OR (SAR231893[Title/Abstract])) OR (SAR- 231893[Title/Abstract])) OR (REGN668[Title/Abstract])) OR (REGN- 668[Title/Abstract])) OR (Dupixent[Title/Abstract])))) OR ((((((Tezepelumab[MeSH Terms]) OR (MEDI-9929[Title/Abstract])) OR (MEDI9929[Title/Abstract])) OR (MEDI-19929[Title/Abstract])) OR (AMG- 157[Title/Abstract])) OR (tezspire[Title/Abstract])) OR (tezepelumab- ekko[Title/Abstract])))) AND ((((Asthma[MeSH Terms]) OR (Asthmas[Title/Abstract])) OR (Asthma, Bronchial[Title/Abstract])) OR (Bronchial Asthma[Title/Abstract])))) AND ((((((((((((Meta-Analysis as Topic[MeSH Terms]) OR (Meta Analysis[Publication Type])) OR (meta analysis[Title/Abstract])) OR (meta analyses[Title/Abstract])) OR (meta-analysis[Title/Abstract])) OR (meta-analyses[Title/Abstract])) OR (data pooling[Title/Abstract])) OR (data poolings[Title/Abstract])) OR (clinical trial overview[Title/Abstract])) OR (clinical trial overviews[Title/Abstract])))) OR </p>

(systematic review[Title/Abstract])) OR (systematic reviews[Title/Abstract]))
OR (indirect treatment comparison [Title/Abstract]))

Embase

#1 'asthma'/exp

#2 'asthma'

#3 'asthma bronchiale' OR 'asthma pulmonale' OR 'asthma, bronchial' OR
'asthmatic' OR 'asthmatic subject' OR 'bronchial asthma' OR 'bronchus asthma' OR
'chronic asthma' OR 'lung allergy'

#4 #1 OR #2 OR #3

#5 'mepolizumab'/exp

#6 'mepolizumab'

#7 'bat 2606' OR 'bat2606' OR 'bosatria' OR 'nucala' OR 'sb 240563' OR 'sb-
240563' OR 'sb240563'

#8 'reslizumab'/exp

#9 'reslizumab'

#10 'cep 38072' OR 'cep38072' OR 'cinquaero' OR 'cinqair' OR 'dcp 835' OR
'dcp835' OR 'sch 55700' OR 'sch55700'

#11 'benralizumab'/exp

#12 'benralizumab'

#13 'biw 8405' OR 'biw8405' OR 'fasentra' OR 'khk 4563' OR 'khk4563' OR 'medi
563' OR 'medi563'

#14 'omalizumab'/exp

#15 'omalizumab'

#16 'aomaishu' OR 'cmab 007' OR 'cmab007' OR 'fb 317' OR 'fb317' OR 'gbr 310' OR 'gbr310' OR 'genolair' OR 'gnr 044' OR 'gnr044' OR 'hu 901' OR 'hu901' OR 'monoclonal antibody E 25' OR 'monoclonal antibody E25' OR 'olizumab' OR 'omalizumab alfa' OR 'omalizumab alpha' OR 'omlyclo' OR 'rg 3648' OR 'rg3648' OR 'rhumab 25' OR 'rhumab e25' OR 'sti 004' OR 'sti004' OR 'syn 008' OR 'syn008' OR 'tev 45779' OR 'tev45779' OR 'xolair'

#17 'dupilumab'/exp

#18 'dupilumab'

#19 'bat 2406' OR 'bat2406' OR 'dupixent' OR 'regn 668' OR 'regn668' OR 'sar 231893' OR 'sar231893'

#20 'tezepelumab'/exp

#21 'tezepelumab'

#22 'amg 157' OR 'amg157' OR 'medi 9929' OR 'medi9929' OR 'tezepelumab ekko' OR 'tezepelumab-ekko' OR 'tezspire'

#23 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22

#24 #4 AND #23

Cochrane Library

#1 MeSH descriptor: [Mepolizumab] explode all trees

#2 MeSH descriptor: [Reslizumab] explode all trees

#3 MeSH descriptor: [Benralizumab] explode all trees

#4 MeSH descriptor: [Omalizumab] explode all trees

#5 Xolair

#6 MeSH descriptor: [Dupilumab] explode all trees

#7	MeSH descriptor: [Tezepelumab] explode all trees
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	MeSH descriptor: [Asthma] explode all trees
#10	Asthma, Bronchial
#11	Asthmas
#12	Bronchial Asthma
#13	#9 OR #10 OR #11 OR #12
#14	#8 AND #13
Web of Science	
TS = (Mepolizumab OR Reslizumab OR Benralizumab OR Omalizumab OR Dupilumab OR Tezepelumab) AND TS = (Asthma)	
Scopus	
(TITLE-ABS-KEY (asthma)) AND ((TITLE-ABS-KEY (mepolizumab) OR TITLE-ABS-KEY (reslizumab) OR TITLE-ABS-KEY (benralizumab) OR TITLE-ABS-KEY (omalizumab) OR TITLE-ABS-KEY (dupilumab) OR TITLE-ABS-KEY (tezepelumab)))	