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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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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,

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

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

PROSPERO registration number: CRD42024607393.

Keywords: biologics, severe asthma, umbrella review, protocol

Article Summary

Strengths and limitations of this study

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

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

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

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

1 INTRODUCTION

Asthma is a prevalent chronic respiratory disease characterized by chronic airway inflammation and airway hyperresponsiveness. It often has recurrent wheezing, shortness of breath, chest tightness, cough and other symptoms.[1] Asthma is a serious global health problem, affecting about 300 million

people worldwide and causing about 250,000 deaths annually.[2] What's worse, patients with severe asthma have more severe symptoms, more frequent exacerbations, and more serious medication side effects, which can interfere with patient's daily life, sleep, and physical activity.[3] A Dutch study showed that about 3.7% of people with asthma have severe asthma.[4] In addition, severe asthma leads to very high medical costs. In a Canadian study, severe asthma accounts for more than 60% of the cost of asthma.[5]

Severe asthma means patients that remain uncontrolled despite adhering to maximal optimized high-dose inhaled corticosteroids (ICS)/long-acting beta-agonists(LABA) treatment and management of associated factors, or that worsen when high-dose treatment is decreased.[6] For these patients, add-on therapy, mainly emerging biologics, are needed to provide new hope for the treatment of severe asthma. Biologics can block the immuno-inflammatory cascade in the pathological course of severe asthma by precisely targeting inflammatory cytokines.[6] Biologics for severe asthma mainly include anti-immunoglobulin E (anti-IgE) treatment (omalizumab), anti-interleukin-5/5Rα (anti-IL5/5Rα) treatment (mepolizumab, reslizumab, benralizumab), anti-interleukin-4Rα (anti-IL4Rα) treatment (dupilumab), and anti-thymic stromal lymphopoietin (anti-TSLP) treatment (tezepelumab). In previous studies, biologics have been shown to be beneficial for severe asthma, which can reduce the frequency of acute exacerbations and hospitalization, improve lung function and quality of life, and decrease the use of systemic corticosteroids.[7][8][9]

Recently, there are many systematic reviews and meta-analyses (SRs/MAs) have shown the efficacy of biologics for severe asthma. Nevertheless, it was also mentioned in the SRs/MAs that the reliability of the results may be affected by the heterogeneity among studies and other risks of bias. Methodological quality, reporting quality and evidence quality of these SRs/MAs are still unclear.

The umbrella review can evaluate the overall quality of relevant SRs/MAs in detail, providing high-quality evidence for clinical practice. However, no umbrella reviews or overviews on this topic have been found. Therefore, it is necessary to conduct an umbrella review to evaluate and summarize the published SRs/MAs.

In this umbrella review, the reporting quality, methodological quality and evidence quality of relevant SRs/MAs will be evaluated through applying Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement, A MeaSurement Tool to Assess Reviews (AMSTAR) 2, and Grading of Recommendation Assessment, Development and Evaluation (GRADE) system, respectively. Meanwhile, we will reassess the efficacy of biologics for patients with severe asthma. Ultimately, this study is expected to provide evidence-based medical evidence for the application of biologics for severe asthma.

2 METHODS AND ANALYSIS

2.1 Design and registration

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

2.2 Inclusion criteria

2.2.1 Types of participants

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

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-IL5/5Rα treatment (mepolizumab, reslizumab, benralizumab), anti-IL4Rα 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,

EMBASE, Cochrane Library, Web of Science, and Scopus databases will be searched for literature. We will also review the conference proceedings. The searched period will run from the date of establishment of databases until November 15, 2024. The search terms are showed as follows: “Mepolizumab ”, “Reslizumab”, “Benralizumab”, “Omalizumab”, “Dupilumab”, “Tezepelumab”, “Asthma”, “systematic review”, and “meta-analysis”. The search strategy in PubMed database are listed in **Table 1**. The full search strategy are 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]))
#4	#1 AND #2 AND #3

2.5 Study selection

After duplicate removal, 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 applied 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 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**.

2.6 Data extraction

Data extraction will be conducted by two researchers (BX and YH). We will extract information from eligible SRs/MAs.

The extracted information of SRs/MAs include name of first author, year of publication, title of SRs/MAs, country, database searched, number of clinical studies, sample size per group, duration of disease, average age per group, gender ratio per group, type and dose of biologics, treatment duration, type of comparisons, 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.

2.7 Quality assessment

2.7.1 Reporting quality assessment

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

2.7.2 Methodological quality assessment

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

2.7.3 Quality of evidence assessment

In terms of quality of evidence, we will apply the GRADE system to assess in detail.[14][15] It will be classified into four grades: high, moderate, low, and critically low. The upgrading factors of the quality of evidence include large effect size, residual confounding, and dose-response relationship, while the degrading factors include limitations of the study, inconsistency, indirectness, publication 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

the application of biologics for severe asthma and provide a reference for clinical practice.

However, this study has some limitations. Firstly, only articles in English will be included in this study and important studies published in other languages may be omitted. Secondly, some subjective factors may have an effect on the evaluation of literature quality. We will minimize the interference of other factors as much as possible and evaluate the quality of literature according to standards.

PATIENT AND PUBLIC INVOLVEMENT

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

ETHICS AND DISSEMINATION

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

Author affiliations

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[2]The First Clinical Medical School, Henan University of Chinese Medicine, Zhengzhou, Henan, China.

Author contributions

QX designed the study, submitted the registration to PROSPERO, and wrote the manuscript. QX and BX completed the search strategy. QX and YH revised the language. MW is responsible for directing the overall study. All authors approved the manuscript.

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Competing interests

None declared.

Patient and public involvement

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

Patient consent for publication

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

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

Supplemental material

The details of the PRISMA-P checklist and the search strategy can be viewed in Supplemental material.

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Figure Legends

Figure 1 Flow chart diagram of study selection.

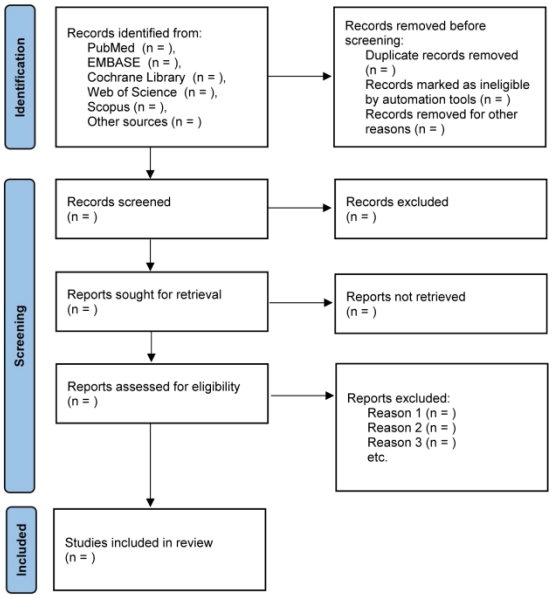

Figure 1 Flow chart diagram of study selection.

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), any 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
((((((((((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 (systematic review[Title/Abstract])) OR (systematic reviews[Title/Abstract]))

Supplementary Material

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

Supplementary Material

#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

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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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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

will evaluate the reporting quality, methodological quality and evidence quality of these SRs/MAs using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, A MeaSurement Tool to Assess Systematic Reviews (AMSTAR) 2, and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, respectively. Additionally, the re-meta-analysis of outcomes will be performed using R software (version 4.3.3).

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

PROSPERO registration number: CRD42024607393.

Keywords: biologics, severe asthma, umbrella review, protocol

Article Summary

Strengths and limitations of this study

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

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

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

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

1 INTRODUCTION

Asthma is a prevalent chronic respiratory disease characterized by airway inflammation and airway hyperresponsiveness. It often presents with recurrent wheezing, shortness of breath, chest tightness, cough, and other symptoms.[1] Asthma is a serious global health problem, affecting about 300 million

people worldwide and causing about 250,000 deaths annually.[2] Additionally, and more importantly, patients with severe asthma have more significant symptoms, more frequent exacerbations, and more serious adverse effects of medications, which can interfere with patients' daily life, sleep, and physical activity.[3] A Dutch study reported that about 3.7% of people with asthma suffer from severe asthma.[4] Furthermore, severe asthma is associated with higher healthcare expenditures. A Canadian study demonstrated that severe asthma accounts for over 60% of total asthma-related costs.[5]

Severe asthma refers to patients who remain uncontrolled despite adhering to maximal optimized high-dose inhaled corticosteroids (ICS)/long-acting beta-agonists (LABA) treatment and management of associated factors, or who worsen when high-dose treatment is decreased.[6] For these patients, add-on therapy, mainly emerging biologics, are needed to provide new hope for the treatment of severe asthma. Biologics can modulate the immuno-inflammatory cascade in the pathological course of severe asthma by precisely targeting inflammatory cytokines.[6] Biologics for severe asthma mainly include anti-immunoglobulin E (anti-IgE) treatment (e.g., omalizumab), anti-interleukin-5/5Rα (anti-IL-5/5Rα) treatment (e.g., mepolizumab, reslizumab, benralizumab), anti-interleukin-4Rα (anti-IL-4Rα) treatment (e.g., dupilumab), and anti-thymic stromal lymphopoietin (anti-TSLP) treatment (e.g., tezepelumab). In previous studies, biologics have been shown to be beneficial for severe asthma, which can reduce the frequency of acute exacerbations and hospitalizations, improve lung function and quality of life, and decrease reliance on systemic corticosteroids.[7][8][9]

Recently, numerous systematic reviews and meta-analyses (SRs/MAs) have demonstrated the efficacy of biologics for severe asthma. However, these SRs/MAs also highlighted potential limitations. The reliability of the results may be affected by the heterogeneity among studies and

other risks of bias. The methodological, reporting, and evidence quality of these SRs/MAs remain unclear. The umbrella review can evaluate the overall quality of relevant SRs/MAs in detail, thereby providing high-quality evidence for clinical practice. To date, no umbrella reviews have been published on this topic, underscoring the need for this study to synthesize existing evidence.

In this umbrella review, the reporting, methodological, and evidence quality of relevant SRs/MAs will be evaluated through using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, A MeaSurement Tool to Assess Systematic Reviews (AMSTAR) 2, and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, respectively. Additionally, we will re-evaluate the efficacy of biologics for patients with severe asthma. Ultimately, this study aims to provide evidence-based medical analysis and summary for the use of biologics in severe asthma.

2 METHODS AND ANALYSIS

2.1 Design and registration

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

2.2 Inclusion criteria

2.2.1 Types of participants

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

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-5/5Rα treatment (mepolizumab, reslizumab, benralizumab), anti-IL-4Rα 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

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 and the European Respiratory Society International Congress will also be searched. The search period will cover 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 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 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

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. The extracted information of SRs/MAs includes name of first author, year of publication, title of SRs/MAs, country, database searched, number of clinical studies, sample size 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.

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

2.7 Quality assessment

All quality assessments will be conducted by two independent reviewers (QX and YH). Discrepancies will be resolved by consulting a third reviewer (MW). Before the quality assessment process, all reviewers will participate in a training session focused on the use of these quality

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

2.7.1 Reporting quality assessment

The reporting quality of the included SRs/MAs will be evaluated using the PRISMA 2020 statement.[12] It consists of 27 items and is scored as follows. A complete report is worth 1 point, a partial report is worth 0.5 points, and an incomplete report is worth 0 points. If all required content is reported, the item will be classified as "complete report", if ≥50% of the reported content is reported with some key information missing, it will be classified as "partial report", if <50% of the reported content is reported or critical elements are missing, it will be classified as "incomplete report". The total score of PRISMA statement is 27 points. In the final evaluation, a score of ≤15 indicates that the report has relatively serious information defects, a score of 15.5-21 indicates that the report has some defects, and a score of 21.5-27 indicates that the report is relatively complete.[13]

2.7.2 Risk of bias (Methodological quality) assessment

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

Furthermore, we will assess the risk of bias of primary studies through seven aspects: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias.[15] In our final review, we will report these assessments, discussing their potential impact on the overall

conclusions.

2.7.3 Quality of evidence assessment

In terms of quality of evidence, we will apply the GRADE system to assess.[16][17] 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 limitations of the study, inconsistency, indirectness, publication bias, and imprecision.

2.8 Management of duplicate reports

To address duplicate publications systematically, 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, with discrepancies 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.[18] $P < 0.1$ or $I^2 > 40\%$ indicates significant heterogeneity, and the random-effects model will be used.[19] Or else, 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 text,

tables, and figures. $P < 0.05$ indicates statistical significance.

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

3 DISCUSSION

In recent years, many SRs/MAs have been published. However, concerns have been raised as the generalizability and validity of such analyses. Different study populations and types of original studies, combined with varying degrees of methodological flaws in SRs/MAs, may lead to misleading clinical decisions. Employing the latest evidence-based medicine analysis, the umbrella review based on SRs/MAs provides more robust and reliable evidence for clinical practice and partially compensates for the limitations of individual SRs/MAs. [20]

Asthma is a serious global health problem, and people with severe asthma have more severe symptoms, frequent exacerbations, and significant medical economic burden.[21] In previous SRs/MAs, biologics have demonstrated promising efficacy and safety,[22][23][24] and are considered a promising treatment for severe asthma. Nevertheless, the overall quality of these SRs/MAs is still unclear, promoting the need for an umbrella review. The findings of this review will further strengthen the evidence-based medical basis for the application of biologics in severe asthma and provide guidance for clinical practice.

Sample size is a critical factor influencing the reliability of SRs/MAs. Adequate sample size enhances the precision of effect estimates and reduces the risk of bias, both of which are essential for

high-quality evidence. Therefore, incorporating sample size as an additional factor in the GRADE system can provide a more comprehensive evaluation of the evidence quality. In this study, we will pay special attention to the sample size of included SRs/MAs to ensure the robustness of our findings.

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

PATIENT AND PUBLIC INVOLVEMENT

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

ETHICS AND DISSEMINATION

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

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Author contributions

QX designed the study, submitted the registration to PROSPERO, and wrote the manuscript. QX and

BX completed the search strategy. QX and YH revised the language. MW is responsible for directing the overall study. All authors approved the manuscript.

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Competing interests

None declared.

Patient and public involvement

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

Patient consent for publication

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

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

Supplemental material

The details of the PRISMA-P 2015 checklist and the search strategy can be viewed in Supplemental

material.

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Figure Legends

329 Figure 1 Flow chart diagram of study selection.

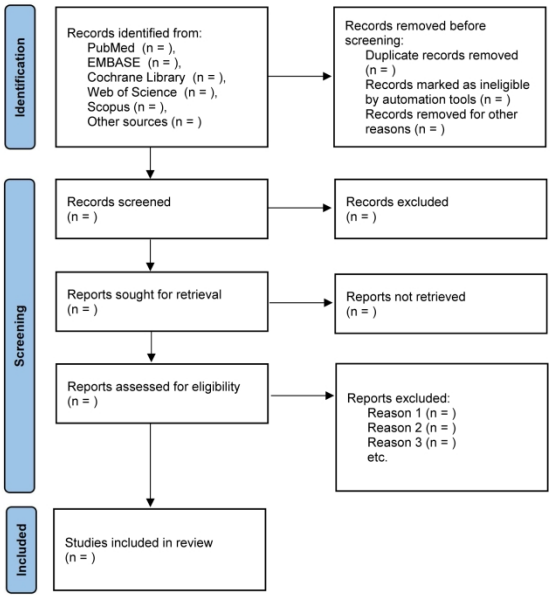

Figure 1 Flow chart diagram of study selection.

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), any 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
((((((((((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

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 '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

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

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Primary Subject Heading:	Respiratory medicine
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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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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

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

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

PROSPERO registration number: CRD42024607393.

Keywords: biologics, severe asthma, umbrella review, protocol

Article Summary

Strengths and limitations of this study

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

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

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

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

1 INTRODUCTION

Asthma is a prevalent chronic respiratory disease characterized by airway inflammation and airway hyperresponsiveness. It often presents with recurrent wheezing, shortness of breath, chest tightness,

cough, and other symptoms.[1] Asthma is a serious global health problem, affecting about 300 million people worldwide and causing about 250,000 deaths annually.[2] Additionally, and more importantly, patients with severe asthma have more significant symptoms, more frequent exacerbations, and more serious adverse effects of medications, which can interfere with patients' daily lives, sleep, and physical activity.[3] A Dutch study reported that about 3.7% of people with asthma suffer from severe asthma.[4] Furthermore, severe asthma is associated with higher healthcare expenditures. A Canadian study demonstrated that severe asthma accounts for over 60% of total asthma-related costs.[5]

Severe asthma refers to patients who remain uncontrolled despite adhering to maximal optimized high-dose inhaled corticosteroids (ICS)/long-acting beta-agonists (LABA) treatment and management of associated factors, or who worsen when high-dose treatment is decreased.[6] For these patients, add-on therapies, mainly emerging biologics, are needed to provide new hope for the treatment of severe asthma. Biologics can modulate the immuno-inflammatory cascade in the pathological course of severe asthma by precisely targeting inflammatory cytokines.[6] Biologics for severe asthma mainly include anti-immunoglobulin E (anti-IgE) treatment (e.g., omalizumab), anti-interleukin-5/5Rα (anti-IL-5/5Rα) treatment (e.g., mepolizumab, reslizumab, benralizumab), anti-interleukin-4Rα (anti-IL-4Rα) treatment (e.g., dupilumab), and anti-thymic stromal lymphopoietin (anti-TSLP) treatment (e.g., tezepelumab). In previous studies, biologics have been shown to be beneficial for severe asthma, as they can reduce the frequency of acute exacerbations and hospitalizations, improve lung function and quality of life, and decrease reliance on systemic corticosteroids.[7][8][9]

Recently, numerous systematic reviews and meta-analyses (SRs/MAs) have demonstrated the efficacy of biologics for severe asthma. However, these SRs/MAs also highlighted potential

limitations. The reliability of the results may be affected by the heterogeneity among studies and other risks of bias. The methodological, reporting, and evidence quality of these SRs/MAs remain unclear. The umbrella review can evaluate the overall quality of relevant SRs/MAs in detail, thereby providing high-quality evidence for clinical practice. To date, no umbrella reviews have been published on this topic, underscoring the need for this study to synthesize existing evidence.

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

2 METHODS AND ANALYSIS

2.1 Design and registration

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

2.2 Inclusion criteria

2.2.1 Types of participants

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

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-5/5Rα treatment (mepolizumab, reslizumab, benralizumab), anti-IL-4Rα 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 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 Respirology 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.

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

2.7 Quality assessment

All quality assessments will be conducted by two independent reviewers (QX and YH). Discrepancies will be resolved by consulting a third reviewer (MW). Before the quality assessment process, all reviewers will participate in a training session focused on the use of these quality assessment tools to enhance inter-rater agreement and minimize bias.

2.7.1 Reporting quality assessment

The reporting quality of the included SRs/MAs will be evaluated using the PRISMA 2020 statement.[12] It consists of 27 items and is scored as follows: a complete report is worth 1 point, a partial report is worth 0.5 points, and an incomplete report is worth 0 points. If all required content is reported, the item will be classified as “complete report”; if ≥50% of the reported content is reported with some key information missing, it will be classified as “partial report”; if <50% of the reported content is reported or critical elements are missing, it will be classified as “incomplete report”. The total score of PRISMA statement is 27 points. In the final evaluation, a score of ≤15 indicates that the report has relatively serious information defects, a score of 15.5-21 indicates that the report has some defects, and a score of 21.5-27 indicates that the report is relatively complete.[13]

Additionally, the PRISMA-NMA 2015 checklist will be used to assess the reporting quality of the included ITCs.[14] It includes 32 items, and the total score is 32 points. Scoring follows the same

criteria as the PRISMA 2020 statement. In the final evaluation, a score of ≤18 indicates that the report has relatively serious information defects, a score of 18.5-25 indicates that the report has some defects, and a score of 25.5-32 indicates that the report is relatively complete.

2.7.2 Risk of bias (Methodological quality) assessment

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

The methodological quality of ITCs will be assessed using the AMSTAR 2 tool, augmented with NMA-specific criteria from the International Society for Pharmacoeconomics and Outcomes Research, Academy of Managed Care Pharmacy, National Pharmaceutical Council (ISPOR-AMCP-NPC) checklist.[16] The four criteria include transitivity assessment, direct and indirect evidence consistency, model selection justification, and cautious interpretation of rankings. Each item is rated yes, partial yes, or no, with overall quality categorized as high, moderate, low, or critically low.

Furthermore, we will assess the risk of bias of primary studies through seven aspects: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias.[17] In our final review, we will report these assessments, discussing their potential impact on the overall 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.

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

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

3 DISCUSSION

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

Asthma is a serious global health problem, and people with severe asthma have more severe symptoms, frequent exacerbations, and significant medical economic burden.[23] In previous SRs/MAs, biologics have demonstrated promising efficacy and safety, and are considered a promising treatment for severe asthma.[24][26] Nevertheless, the overall quality of these SRs/MAs is still unclear, prompting the need for an umbrella review. The findings of this review will further

strengthen the evidence-based medical basis for the application of biologics in severe asthma and provide guidance for clinical practice.

Sample size is a critical factor influencing the reliability of SRs/MAs. Adequate sample size enhances the precision of effect estimates and reduces the risk of bias, both of which are essential for high-quality evidence. Therefore, incorporating sample size as an additional factor in the GRADE system can provide a more comprehensive evaluation of the quality of evidence. In this study, we will pay special attention to the sample size of included SRs/MAs to ensure the robustness of our findings.

However, this study has some limitations. Firstly, we will include only articles in English and exclude studies published in other languages. As most databases and literature resources are in English, language restrictions help ensure data accuracy and consistency, thereby facilitating precise data extraction and analysis. Secondly, some subjective factors may affect the evaluation of literature quality.

PATIENT AND PUBLIC INVOLVEMENT

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

ETHICS AND DISSEMINATION

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

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Author contributions

Qionghua Xiao designed the study, submitted the registration to PROSPERO, and wrote the manuscript. Qionghua Xiao and Bingyu Xue completed the search strategy. Qionghua Xiao and Yuanming Huang revised the language. Minghang Wang is responsible for directing the overall study. Minghang Wang is the guarantor.

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Competing interests

None declared.

Patient and public involvement

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

Patient consent for publication

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

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

Supplemental material

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

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Figure Legends

Figure 1 Flow chart diagram of study selection.

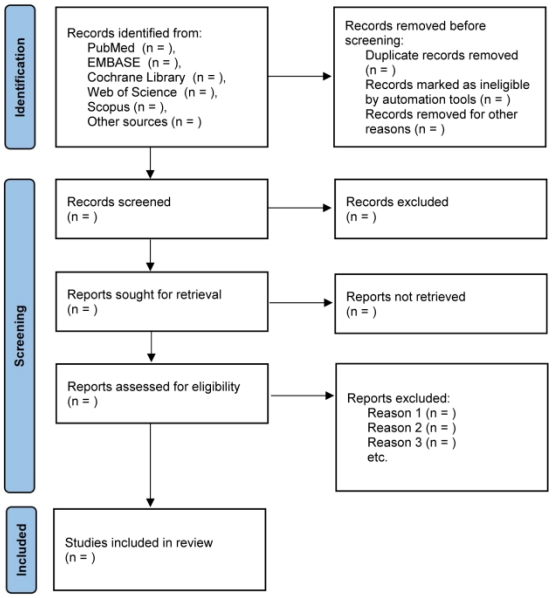

Figure 1 Flow chart diagram of study selection.

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), any 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
((((((((((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

(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 '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

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)))	