

Review Article

Biologics for moderate-to-severe eosinophilic asthma in children: a network meta-analysis

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Received July 13, 2026; Accepted September 14, 2026; Epub October 15, 2026; Published October 30, 2026

Abstract: Pediatric moderate-to-severe eosinophilic asthma (EA) is a severe refractory condition with limited response to conventional therapy. Although biologic agents offer new treatment options, comparative data on their efficacy and safety remains insufficient. This network meta-analysis evaluated Omalizumab, Mepolizumab, Benralizumab, Lebrikizumab, and Dupilumab in children with moderate-to-severe EA. A systematic search of PubMed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang, and VIP databases was conducted up to March 31, 2026. Randomized controlled trials comparing these biologics with placebo or active control/standard care were included. The primary outcome was annual asthma exacerbation rate; secondary outcomes included FEV₁ changes, adverse events (AEs), and serious adverse events (SAEs). Network meta-analyses were performed using a consistency model in Stata 16.0. Effect sizes are reported as risk ratios (RR) or standardized mean differences (SMD) with 95% confidence intervals. Treatment rankings were based on SUCRA values. Thirteen RCTs (n = 3,269) were included. Dupilumab (RR = 0.34), Omalizumab (RR = 0.59), and Mepolizumab (RR = 0.73) significantly reduced exacerbations versus placebo. Dupilumab was associated with a lower exacerbation rate than Omalizumab (RR = 0.58) and Mepolizumab (RR = 0.47). SUCRA rankings favored Dupilumab (94.1%) for exacerbation reduction; however, as Dupilumab's ranking is based on a single trial, this probability carries high uncertainty and should not be equated with proven clinical superiority. Only Omalizumab significantly improved FEV₁ (SMD = 1.00). Mepolizumab showed the highest AE risk, while Omalizumab had the best safety profile (SUCRA = 87.8%). SAE frequencies were comparable across treatments; however, due to extreme event sparsity across trials, these network estimates carry substantial statistical uncertainty and should be interpreted with caution. These comparative findings should be regarded as hypothesis-generating given the limited study count, heterogeneity in control group background therapies, and lack of direct head-to-head trials. Preliminary indirect evidence suggests Dupilumab may hold potential advantages for exacerbation reduction, while Omalizumab shows tentative benefits for lung function and safety. Future head-to-head trials are required to confirm these tentative observations. Treatment selection must remain individualized.

Keywords: Eosinophilic asthma, children, biologics, network meta-analysis, efficacy, safety

Introduction

Asthma is a relatively common chronic lung disease in children, and generally presents with increased airway reactivity, intermittent narrowing of the airways, and recurrent symptoms such as wheezing, shortness of breath and chest tightness [1]. According to statistics released by the 2021 Global Burden of Disease (GBD) study, as of 2021, there were approximately 95.7 million cases of juvenile asthma globally, and the age-standardized rate is about 4,758 per 100,000 people. Although most young people can be well-managed by conventional therapy (low-to-medium dose inhaled

corticosteroids), 2%-10% of young people have severe asthma [2, 3]. Even after receiving intensive care, children with severe asthma who have been treated with high-dose inhaled corticosteroids and long-acting beta-2 agonists still suffer from recurrent acute exacerbations, reduced respiratory function and a significant decline in quality of life; these symptoms place a heavy financial and psychological burden on families and society [4].

Severe asthma shows considerable heterogeneity, and the dominant type of inflammation in Type 2 (T2) asthma is particularly common among children [5]. T2 inflammation is charac-

terized by the excessive production of cytokines such as interleukin (IL)-4, IL-5 and IL-13, which can lead to eosinophilic infiltration, increased immunoglobulin E (IgE) levels and airway hyperreactivity. Research has shown that 50%-90% of patients with severe asthma exhibit features of eosinophilic inflammation, and eosinophilic asthma (EA) has emerged as one of the most common phenotypes of asthma in children [6]. However, young people with EA generally have a reduced response to high-dose inhaled glucocorticoids and combination controller therapy, so new and more targeted therapeutic options are urgently needed.

In recent years, biologic agents that target key components of the T2 inflammatory pathway have emerged rapidly and are now essential treatment options for severe asthma in young people. At present, several monoclonal antibodies have been approved for use as add-on therapy in childhood asthma, including Omalizumab (anti-IgE), Mepolizumab (anti-IL-5), Benralizumab (anti-IL-5R α), and Dupilumab (anti-IL-4R α). Many randomized controlled trials (RCTs) have shown that these biologics can reduce the frequency of acute exacerbations, improve pulmonary function and asthma control compared with placebo, and generally have a favorable safety profile [7-11]. The 2025 revision of the GINA guidelines has added these biologics to the Class 5 therapeutic approach and now considers them one of the first-line options for severe pediatric asthma treatment [12].

However, there are relatively few direct comparisons in the existing literature on the efficacy and safety of biologics for pediatric asthma. Currently, most of the available evidence comes from RCTs that compare single drugs with a placebo, and these studies have considerable heterogeneity in terms of participant characteristics, biomarker selection criteria and clinical end points; thus, the results are difficult to synthesize using conventional pairwise analyses. Although several systematic reviews and network meta-analyses (NMAs) have attempted to broadly evaluate biologics for pediatric asthma [13-15], these previous works are still not comprehensive in their inclusion of various therapeutic agents, and systematic assessments focusing specifically on the "EA" phenotype are currently lacking. Given

current state of research, this study aimed to conduct a NMA of all randomized controlled trials (RCTs) published up to March 31, 2026, that evaluated various biologic therapies in children with EA. Specifically, we comprehensively compared and ranked five biologics according to their efficacy in improving pulmonary function, controlling asthma symptoms, reducing exacerbations, and enhancing quality of life, as well as their safety, thereby providing evidence to inform personalized treatment selection.

Methods

Inclusion and exclusion criteria

Inclusion criteria: (1) Population: Children and adolescents aged ≤ 18 years, clinically diagnosed with EA characterized by increased peripheral blood eosinophil counts (BEC) (typically ≥ 150 -300 cells/mm³, varying according to study parameters) and/or indications of bronchial eosinophilic infiltration, or identified as a type 2 high-expression group according to clinical protocols; (2) Intervention: Limited to one or more of the following biological treatments versus placebo; (3) Outcome measures: At least one primary endpoint has been recorded, including annual asthma attack frequency, Asthma Control Questionnaire (ACQ) scores, asthma-specific quality of life, and monitoring of adverse events (AEs) and severe adverse events (SAEs) for the whole cohort; (4) Study design: randomized controlled trials (RCTs); (5) Language: restricted to publications written and published in English or Chinese.

Criteria for exclusion include: (1) Unsuitable research subjects; (2) Ineligible interventions; (3) Lack of relevant outcomes for this study or inability to obtain reliable data; (4) Non-RCTs, such as basic research, case reports, descriptive series, reviews, systematic reviews or meta-analyses; (5) Duplicate publications; (6) Articles for which the full text could not be obtained after multiple attempts.

The study protocol was retrospectively registered with the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) on August 5, 2026 (Registration number: INPLASY202680024). Data extraction and analyses commenced prior to formal protocol registration. This network

meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analyses (PRISMA-NMA). The completed PRISMA-NMA checklist is provided as [Supplementary Table 1](#).

Literature review

A series of systematic and comprehensive literature searches were conducted in PubMed, Embase, Web of Science, the Cochrane Library, CNKI, Wanfang Data Knowledge Service Platform (WANFANG), and the VIP database using a combination of free-text and MeSH keywords related to “asthma”, “children”, “adolescents”, “eosinophils”, “biologics” and specific drug formulations. The English search string was, for example: (“Omalizumab” OR “Mepolizumab” OR “Benralizumab” OR “Dupilumab” OR “Lebrikizumab” OR “Tezepelumab”) AND (“child” OR “pediatric” OR “adolescent”) AND (“asthma” OR “eosinophilic asthma”). The Chinese search used term pairs such as “Omalizumab”, “Mepolizumab”, “Benralizumab”, “Dupilumab”, “Lebrikizumab”, “Tezepelumab”, “eosinophils” and “asthma”. Additionally, the relevant reviews and citation lists from previous systematic reviews were manually examined, and grey literature (such as conference abstracts) was collected to find all possible studies. The database search was completed on March 31, 2026.

Two researchers independently screened the records according to the given inclusion and exclusion criteria. After eliminating the duplicate entries using EndNote X9, they reviewed the titles and abstracts to exclude research that clearly did not meet the recruitment requirements. Then, among the studies that appeared to meet the inclusion criteria, the complete documents were obtained and examined to determine whether they were suitable for inclusion in the review according to the recruitment standards. The two investigators collected related studies and verified the results independently. Any disagreements were resolved through discussion with the third co-author.

Data extraction and outcome measures

The two investigators independently gathered data from the selected papers. The extracted

data included the first author, publication year, participant characteristics, precise details of the research protocol, specific definitions of control group regimens (categorized into placebo plus standard-of-care [SOC] background therapy vs. active comparator controls, such as budesonide suspension), and outcomes. Data were recorded using a standardized electronic spreadsheet. Disagreements were resolved through discussion with a third author.

Outcome measures included the frequency of annual asthma exacerbations, forced expiratory volume in one second relative to predicted values (FEV1), Asthma Control Questionnaire (ACQ) scores, forced vital capacity (FVC), asthma-specific quality of life, inflammatory biomarker levels, and incidence of adverse events (AEs) and serious adverse events (SAEs) in the entire cohort.

Assessment of the study quality

Two investigators assessed the methodological quality of the enrolled trials according to the Cochrane Risk of Bias tool version 2.0 (RoB 2.0) and evaluated the following five domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result [16]. Each domain was rated as “low risk”, “high risk”, or “some concerns” based on the adequacy of reporting in the included studies. The risk of bias assessment results were visualized using RevMan 5.3 software to generate risk of bias graphs and risk of bias summary figures. Two investigators independently evaluated and cross-checked the results, and any disagreements during the evaluation process were resolved through discussion with a third author.

Statistical analysis

Review Manager 5.3 was employed to assess the quality of the included trials and generate Cochrane risk-of-bias plots. Stata 16.0 was used to process the data, and the network command was employed. Dichotomous variables were presented as risk ratios (RR), continuous variables were standardized mean differences (SMD), and in both cases, 95% confidence intervals (95% CI) were reported. Statistical significance was set at $P < 0.05$. A

network evidence map was constructed, where the number of nodes corresponds to different treatments, the size of a node indicates the total sample size for that treatment, and an edge connecting two nodes represents a direct comparison between the two therapies; the thickness of the edge shows how many studies have included both treatments. The existence of a closed loop in the interventions suggests both direct and indirect evaluations; inconsistency tests need to be conducted in these cases to determine whether direct and indirect outcomes are consistent. As no closed loops appeared for any of the outcome indicators in this study, no heterogeneity test was carried out; thus, the results were directly fitted by a consistency model. The results of network meta-analysis are shown in a league table. A finding is considered statistically significant if the 95% confidence interval (CI) for the risk ratio (RR) of a dichotomous variable does not include 1, or if the 95% CI for the standardized mean difference (SMD) of a continuous variable does not include 0. According to the surface under the cumulative ranking curve (SUCRA), the different treatment options were ranked; a higher SUCRA value indicates better therapeutic effects and a relatively larger proportion of other treatments; a lower SUCRA value suggests poor efficacy. Finally, a comparison-adjusted funnel plot of the included studies was generated to determine whether there were small-sample biases or publication bias.

Sensitivity and specificity analysis

To examine the stability of the results from network meta-analysis, sensitivity and specificity analyses were conducted for both treatment outcomes (annual incidence of acute asthma attacks) and safety indicators (frequency of adverse events). (1) Sensitivity analysis: The leave-one-out method was employed to sequentially exclude each study, followed by a rerun of the network meta-analysis to observe any shifts in the size of the pooled effect and the position of SUCRA. (2) Specificity analysis: By modifying selection criteria, Chinese publications and small-scale trials (with fewer than 200 participants) were excluded individually, and then a network meta-analysis was conducted again to determine if there were any changes in the size of the pooled effect and

the rank of SUCRA; thus, the robustness of the results under different selection criteria was confirmed.

Results

Results of literature inclusion

According to the above research framework, a comprehensive search of the seven representative Chinese and international databases yielded a total of 1,712 unique references, including PubMed (n = 552), Cochrane Library (n = 289), Embase (n = 176), Web of Science (n = 128), CNKI (n = 352), WANFANG (n = 124) and VIP (n = 91). After removing 915 duplicates, 797 articles were screened by title and abstract, of which 504 were excluded (mainly due to: 278 non-RCT studies, 126 articles with inappropriate interventions, and 100 basic research studies and other types). Among the 293 remaining manuscripts, full texts were obtained and assessed; 280 were excluded (the primary reasons being non-conforming outcome measures in 193 studies, ongoing studies in 36 studies, and unavailability of full text in 51 studies). A total of 13 studies were included in this network meta-analysis [7, 9, 17-27]. The specific selection process and reasons for the rejection are shown in **Figure 1**.

General features of the included studies

A total of 13 RCTs [7, 9, 17-27] involving 3,269 participants were included in the evaluation. All the control groups were placebos or standard combination therapies; the drugs in the treatment groups mainly included budesonide suspension, beclomethasone dipropionate plus salbutamol, and specific treatment plans and durations varied among the studies. In the treatment groups, eight trials compared Omalizumab with placebo or active controls [7, 17-19, 21, 22-24], and the other studies investigated Dupilumab [20, 27], Mepolizumab [9], Lebrikizumab [25], and Benralizumab [26] versus placebo. All included studies enrolled pediatric and adolescent subjects with moderate-to-severe asthma and elevated type 2 biomarkers or a BEC of ≥ 150 cells/mm³. Although tezepelumab was included in the a priori search protocol, no pediatric RCTs met the inclusion criteria and therefore could not be used in the final meta-analysis. The baseline participant characteristics and detailed control

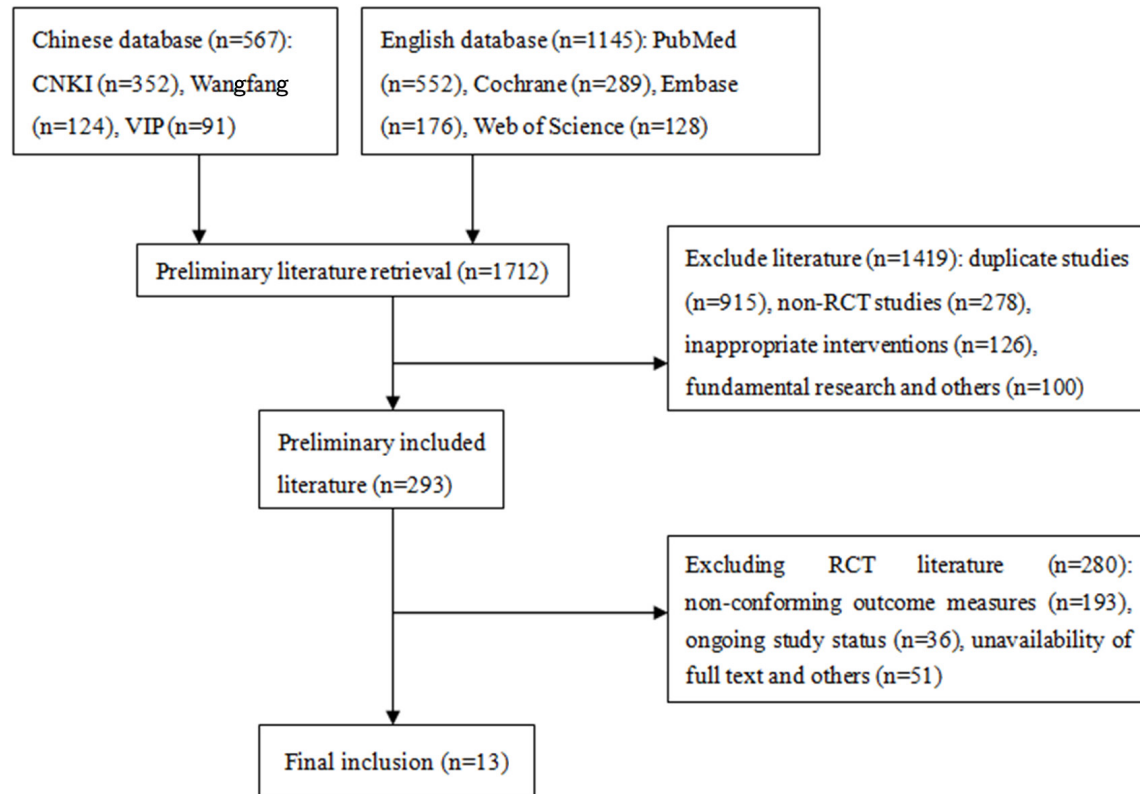


Figure 1. Literature search and selection process.

group definitions of the included studies are shown in **Table 1**.

Age reporting across the included RCTs showed heterogeneity in age reporting, presented as mean $\pm$ SD in some trials and median (IQR/range) in others (**Table 1**). This reporting discrepancy reflects underlying variations in study population age distributions across trials—ranging from broad pediatric cohorts (6-17 years) to narrower subpopulations. Such reporting heterogeneity limits precise age-standardized pooled comparisons and may constrain the generalizability of our efficacy and safety estimates across specific pediatric age subgroups, particularly in younger children (< 6 years) who were underrepresented in the primary trials.

Assessment of the risk of bias

For the included studies, we assessed the quality using RoB 2.0. In the domain of randomization process, all 13 studies [7, 9, 17-27] were rated as low risk. In the domain of deviations from intended interventions, 9 studies [9,

20-27] were rated as low risk because they achieved blinding of participants and personnel, while 4 studies [7, 17-19] were rated as having “some concerns” because the difference in administration routes (subcutaneous injection vs. inhaled corticosteroids) made double-blinding difficult to implement. In the domain of missing outcome data, all studies were rated as low risk. In the domain of measurement of the outcome, 9 studies [9, 20-27] were rated as low risk because outcome assessors were blinded, while 4 studies [7, 17-19] were rated as having “some concerns” because blinding of outcome assessors was not explicitly reported. In the domain of selection of the reported result, all studies were rated as low risk. Overall, 9 studies [9, 20-27] were rated as low risk across all five domains, indicating a low overall risk of bias; 4 studies [7, 17-19] were rated as having “some concerns” in the domains of deviations from intended interventions and measurement of the outcome due to difficulties in implementing blinding. The risk of bias for the included studies was assessed using RevMan 5.3 soft-

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Table 1. Basic information in the included studies

Literature	Age		Number of cases		Treatment		Intervention period (weeks)
	Experimental	Control	Experimental	Control	Experimental	Control	
Chen F 2023 [7]	8.39 ± 1.03	8.52 ± 1.12	44	44	Omalizumab	Active Control: Budesonide suspension	16
Jackson DJ 2022 [9]	10.0 (9.0-13.0)	11.0 (9.0-13.0)	146	144	Mepolizumab	Placebo	52
Ge WJ 2024 [17]	6.62 ± 1.25	6.54 ± 1.18	49	49	Omalizumab	Active Control: Budesonide suspension	16
Zhou W 2024 [18]	5.94 ± 1.31	5.68 ± 1.38	43	43	Omalizumab	Active Control: Budesonide suspension	16
Zhang XN 2022 [19]	14.23 ± 1.22	14.45 ± 1.27	55	59	Omalizumab	Active Control: Budesonide suspension	24
Bacharier LB 2021 [20]	8.9 ± 1.6	9.0 ± 1.5	175	84	Dupilumab	Placebo	52
Teach SJ 2015 [21]	10.3 (2.99)	10.1 (3.06)	259	89	Omalizumab	Placebo + SOC (Standard asthma care)	12
Busse WW 2011 [22]	10.9 ± 3.6	10.8 ± 3.4	208	211	Omalizumab	Placebo + SOC (ICS dose-reduction protocol)	48
Berger W 2003 [23]	9.4 (5-12)	9.5 (6-12)	225	109	Omalizumab	Placebo + SOC (Concomitant ICS therapy)	28
Lanier B 2009 [24]	8.7 (1.7)	8.4 (1.7)	421	207	Omalizumab	Placebo + SOC (Moderate-to-high ICS)	52
Szeffler SJ 2022 [25]	14.2 (1.5)	14.1 (1.7)	113	117	Lebrikizumab	Placebo	52
Busse WW 2021 [26]	15.5 ± 1.63	15.6 ± 1.39	14	11	Benralizumab	Placebo	108
Fiocchi AG 2023 [27]	8.9 ± 1.6	9.6 ± 1.6	236	114	Dupilumab	Placebo	52

Note on Age Reporting: Patient age is presented as mean ± SD for studies reporting normally distributed data, and as median (IQR or range) for studies reporting skewed data. SOC = Standard-of-Care background therapy.

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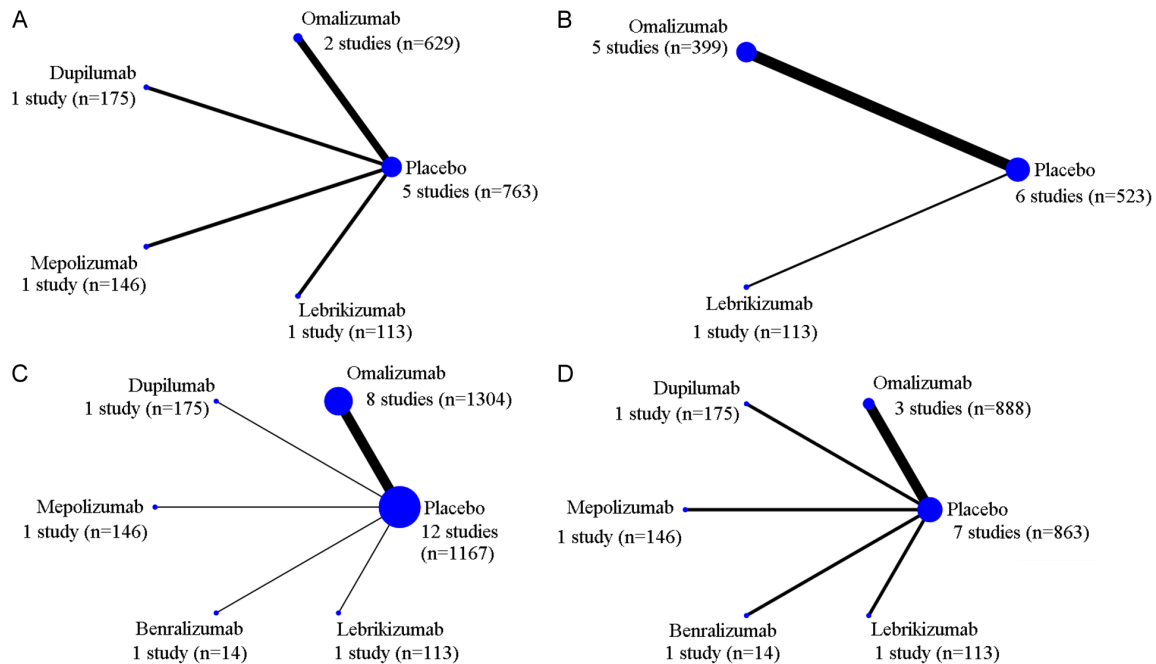


Figure 2. Network plot of the meta-analysis. A. Annual rate of acute asthma exacerbations; B. Change in FEV₁; C. Frequency of negative outcomes; D. Frequency of major negative outcomes forced expiratory volume in one second relative to predicted values (FEV₁).

Table 2. Network meta-analysis of the frequency of acute asthma attacks per year

Intervention	RR (95% CI)				
	Dupilumab	Omalizumab	Lebrizumab	Mepolizumab	Placebo
Dupilumab	0.00				
Omalizumab	0.58 (0.35-0.95)*	0.00			
Lebrizumab	0.57 (0.28-1.15)	0.97 (0.55-1.72)	0.00		
Mepolizumab	0.47 (0.27-0.81)*	0.81 (0.58-1.13)	0.84 (0.45-1.52)	0.00	
Placebo	0.34 (0.21-0.55)*	0.59 (0.50-0.71)*	0.61 (0.35-1.04)	0.73 (0.55-0.96)*	0.00

Note: *P < 0.05 for the comparison between groups.

ware, and the results are presented in [Supplementary Figure 1](#).

Results of the network meta-analysis

Annual exacerbation rate: (1) Network evidence: Five studies [9, 20, 22, 24, 25] reported the annual rate of acute asthma exacerbations, involving a total of four interventions. As the evidence network did not form a closed loop, the analysis was conducted using a consistency model. The results are shown in **Figure 2A**. (2) As shown in **Table 2**, Dupilumab (RR = 0.34, 95% CI: 0.21-0.55), Omalizumab (RR = 0.59, 95% CI: 0.50-0.71), and Mepolizumab (RR = 0.73, 95% CI: 0.55-0.96) significantly reduced annual exacerbation risk versus

placebo, while Lebrizumab showed a trend toward reduction that did not reach statistical significance (RR = 0.61, 95% CI: 0.35-1.04). Dupilumab was significantly more effective than Omalizumab (RR = 0.58, 95% CI: 0.35-0.95) and Mepolizumab (RR = 0.47, 95% CI: 0.27-0.81). (3) **Figure 3A** presents the SUCRA ranking: Dupilumab (94.1%, 1 study, n = 175) > Lebrizumab (53.6%, 1 study, n = 113) > Omalizumab (50.7%, 2 studies, n = 629) > Mepolizumab (48.2%, 1 study, n = 146) > placebo (3.4%, 5 studies, n = 763). (Caveat: The high SUCRA probability for Dupilumab is derived from a single trial node. SUCRA values generated from sparse evidence networks with few studies per treatment node carry substantial statistical uncertainty and reflect relative

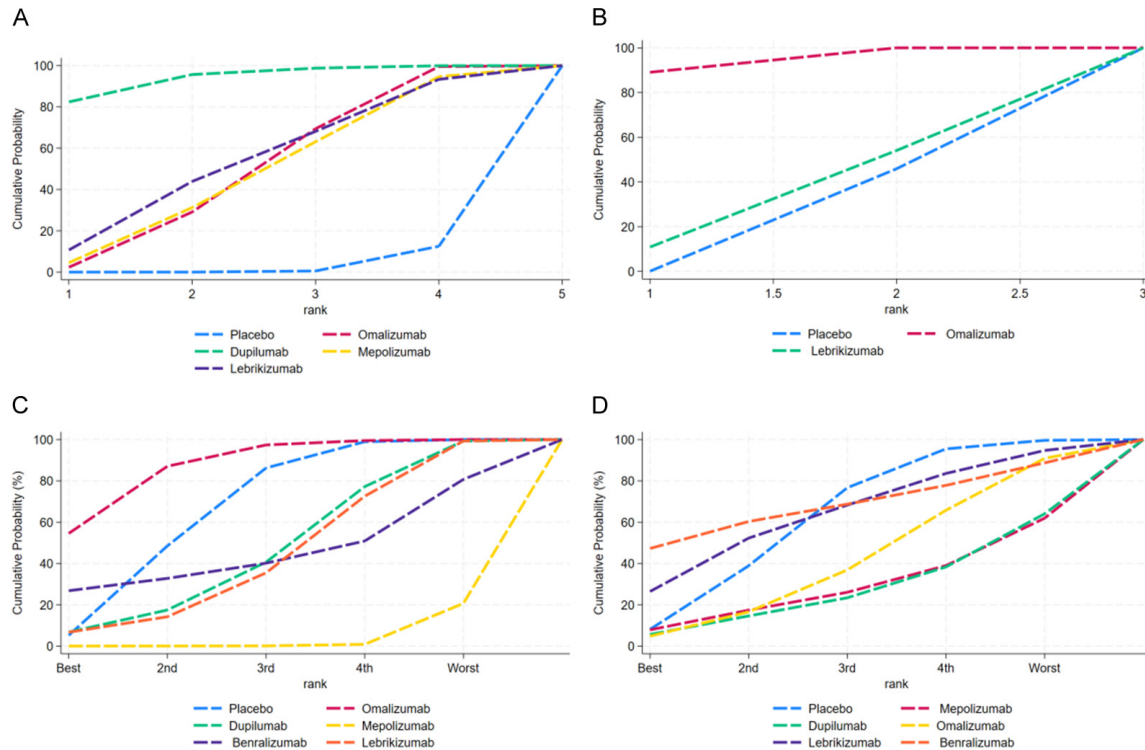


Figure 3. SUCRA plot. Note: A. Annual rate of acute asthma exacerbations; B. Change in FEV_1 ; C. Incidence of adverse events; D. Incidence of serious adverse events. SUCRA, surface under the cumulative ranking curve; SUCRA values indicate rank probability distributions only and should not be equated with absolute magnitude or clinically meaningful differences forced expiratory volume in one second relative to predicted values (FEV_1).

Table 3. Results of the network meta-analysis on changes in FEV_1

Intervention	SMD (95% CI)		Placebo
	Omalizumab	Lebrikizumab	
Omalizumab	0.00		
Lebrikizumab	0.96 (-0.95, 2.87)	0.00	
Placebo	1.00 (0.21, 1.79)*	0.05 (-1.69, 1.78)	0.00

Note: * $P < 0.05$ for the above group comparison.

analysis: The five studies [9, 20, 22, 24, 25] included in the annual acute exacerbation rate outcome were all English-language studies. No additional subgroup analyses were performed due to the limited number of studies per intervention; however, the leave-one-out sensitivity analysis confirmed the robustness of the primary findings.

probability rankings rather than direct, clinically meaningful effect sizes). (4) Robustness assessment: Regarding the annual incidence of acute asthma attacks [9, 20, 22, 24, 25], the NMA was repeatedly conducted by systematically omitting every individual trial. These findings indicated that the RR estimates for Dupilumab varied between 0.31 and 0.38, for Omalizumab between 0.55 and 0.63, and for Mepolizumab between 0.69 and 0.78, where all 95% CIs remained excluded the null. The SUCRA ordering (Dupilumab > Lebrikizumab > Omalizumab > Mepolizumab > Placebo) matched the initial findings entirely. (5) Specificity

Alterations in FEV_1 : (1) Network evidence: Six studies [7, 17-19, 22, 25] reported changes in FEV_1 two interventions. As the evidence network did not form a closed loop, a consistency model was used for analysis. Results are shown in **Figure 2B**. (2) As shown in **Table 3**, Omalizumab demonstrated a significant advantage over placebo in improving FEV_1 (SMD = 1.00, 95% CI: 0.21-1.79), while Lebrikizumab showed no statistically detectable difference versus placebo or Omalizumab ($P > 0.05$). A meta-regression analysis with route of administration (subcutaneous vs. inhalation) as a covariate showed no significant effect on the

Table 4. Results of the network meta-analysis on the incidence of adverse effects

Intervention	RR (95% CI)					
	Mepolizumab	Benralizumab	Lebrikizumab	Dupilumab	Placebo	Omalizumab
Mepolizumab	0.00					
Benralizumab	2.27 (0.37-13.73)	0.00				
Lebrikizumab	2.51 (1.09-5.77)*	1.12 (0.19-6.56)	0.00			
Dupilumab	2.61 (1.15-5.93)*	1.16 (0.20-6.82)	1.04 (0.49-2.23)	0.00		
Placebo	3.22 (1.72-6.05)*	1.43 (0.26-7.78)	1.28 (0.75-2.20)	1.23 (0.73-2.10)	0.00	
Omalizumab	3.71 (1.90-7.23)*	1.65 (0.30-9.08)	1.48 (0.82-2.66)	1.42 (0.79-2.54)	1.15 (0.90-1.46)	0.00

Note: *P < 0.05, comparison among groups.

pooled estimate ($\beta = 0.42$, 95% CI: -0.58-1.42, $P = 0.39$), indicating no statistically significant moderating effect on the pooled FEV₁ estimate. This suggests that differences in route of administration did not substantially confound objective lung function outcomes for Omalizumab. (3) **Figure 3B** displays the SUCRA ranking: Omalizumab (91.9%) > Lebrikizumab (33.6%) > placebo (24.5%).

Incidence of adverse events: (1) Network evidence: Twelve investigations [7, 9, 17-26] documented the occurrence of adverse events, such as upper respiratory tract infections, local injection-site reactions, gastrointestinal disorders, hematologic abnormalities, coughing, throat irritation, headaches, pharyngitis, contact dermatitis and rash. Five distinct therapies were incorporated; because the evidence network did not form a closed loop, a consistency model was used for evaluation. These findings are depicted in **Figure 2C**. (2) **Table 4** summarizes the NMA results. Mepolizumab showed the highest risk of AEs, significantly higher than Lebrikizumab (RR = 2.51, 95% CI: 1.09-5.77), Dupilumab (RR = 2.61, 95% CI: 1.15-5.93), placebo (RR = 3.22, 95% CI: 1.72-6.05), and Omalizumab (RR = 3.71, 95% CI: 1.90-7.23). No significant differences were observed between Benralizumab and other treatments ($P > 0.05$). (3) **Figure 3C** illustrates the SUCRA ranking for safety: Omalizumab (87.8%) > placebo (67.3%) > Dupilumab (49%) > Benralizumab (46.5%) > Lebrikizumab (45.3%) > Mepolizumab (4.2%). (4) Sensitivity evaluation: Regarding the frequency of AEs [7, 9, 17-26], the NMA was repeated by sequentially omitting every individual study. These findings indicated that the risk of AEs associated with Mepolizumab remained notably greater than that of Omalizumab (RR estimates fluctuating between 3.42 and 3.89, with every

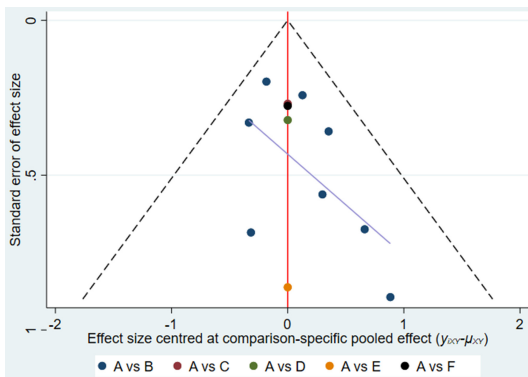
95% CI excluding the null). The SUCRA scores for Omalizumab varied between 85.1% and 90.2%, and the safety hierarchy (Omalizumab > Placebo > Dupilumab > Benralizumab > Lebrikizumab > Mepolizumab) remained consistent with the initial analysis. (5) Sensitivity assessment: Upon removing three Chinese publications [17-19], the risk of Mepolizumab-related AEs remained substantially greater than that for Omalizumab (RR = 3.58, 95% CI: 1.76-7.28) and placebo (RR = 3.11, 95% CI: 1.61-6.02), while the SUCRA order remained consistent. Following the omission of four small-scale trials [7, 17, 18, 26], the RR for Mepolizumab compared to Omalizumab reached 3.65 (95% CI: 1.80-7.41), nearly matching the initial findings (RR = 3.71), and the overall safety hierarchy stayed stable.

Incidence of SAEs: (1) Network evidence: Seven studies [9, 20-22, 24-26] reported the incidence of SAEs, including hospitalization due to acute asthma exacerbations, tic disorders, allergic reactions, tuberculosis, angioedema, and keratitis. A total of five interventions were involved; as the evidence network did not form a closed loop, the consistency model was used for analysis. Results are shown in **Figure 2D**. (2) **Table 5** shows that no significant differences in SAE incidence were observed between any biologic and placebo, or among the biologics ($P > 0.05$). The numerical effect estimates in **Table 5** (e.g., RR = 7.62 for Benralizumab vs. placebo) derive from extreme event sparsity. These data yield extraordinarily wide 95% CIs (0.21-273) and highly unstable relative risks. Consequently, these quantitative network estimates are statistically imprecise and clinically uninterpretable; SUCRA rankings for SAEs must not be used to infer superior safety. (3) **Figure 3D** presents the SUCRA ranking: Benralizumab

Table 5. Outcomes of the network meta-analysis on the incidence of serious adverse events

Intervention	RR (95% CI)					
	Mepolizumab	Dupilumab	Lebrikizumab	Placebo	Omalizumab	Benralizumab
Mepolizumab	0.00					
Dupilumab	2.77 (0.04-176)	0.00				
Lebrikizumab	2.89 (0.04-206)	1.04 (0.05-20.4)	0.00			
Placebo	2.97 (0.08-113)	1.07 (0.15-7.85)	1.04 (0.11-9.59)	0.00		
Omalizumab	3.03 (0.06-139)	1.09 (0.11-11.1)	1.05 (0.08-13.6)	1.02 (0.30-3.39)	0.00	
Benralizumab	22.6 (0.14-3750)	8.16 (0.14-489)	7.92 (0.12-525)	7.62 (0.21-273)	7.54 (0.17-333)	0.00

Note: $P > 0.05$ for all between-group comparisons. Estimates in this table are derived from sparse event counts, including zero-event arms. The resulting extremely wide 95% confidence intervals indicate severe statistical instability. These values are presented for meta-analytic completeness only and should NOT be interpreted as indicative of clinical risk or relative safety differences.


Figure 4. Comparison-adjusted Funnel plot.

(68.6%) > Lebrikizumab (65.1%) > placebo (63.8%) > Omalizumab (43.0%) > Mepolizumab (30.4%) > Dupilumab 29.2%). (Note: This ranking reflects probability distributions under sparse data conditions rather than actual clinical superiority).

Other outcome measures: Some studies reported outcomes, such as quality-of-life indicators and biochemical data, but due to differences in presentation style among the trials, these data were not pooled and only narrative descriptions have been provided. Four studies [17, 19, 24, 27] examined quality-of-life outcomes. Research by Ge et al. [17] and Zhang et al. [19] showed that the improvements in quality-of-life scores before and after Omalizumab treatment was significantly greater than that in the placebo group ($P < 0.05$). Fiochi [27] reported that Dupilumab improved quality of life for children significantly (LSMD = 0.34, 95% CI: 0.16-0.52; $P = 0.0002$). Lanier et al. [24] found that Omalizumab increased the quality of life (LSMD = 0.04) for children, but this difference was not statistically significant ($P = 0.676$). These findings suggest that

Dupilumab improves the quality of life for children with asthma; however, the effect of Omalizumab on improving the quality of life in this group remains unknown. Three studies [7, 17, 18] have examined the concentrations of inflammatory mediators. Research by Ge et al. [17] and Zhou et al. [18] showed that the range of hs-CRP and IL-6 concentrations before and after Omalizumab treatment was significantly larger than that in the placebo group ($P < 0.05$). Zhou et al. [18] and Chen et al. [7] found that the changes in IgG, IgA and IgE levels before and after Omalizumab treatment was significantly higher than that in the placebo group ($P < 0.05$). Therefore, Omalizumab may reduce the levels of inflammatory markers in children with asthma and enhance immune function simultaneously. Meta-regression could not be performed for patient-reported subjective outcomes due to sparse data and inconsistent reporting formats across trials. Because non-identical administration routes introduce an inherent risk of unblinding, performance bias cannot be ruled out and may have inflated perceived benefits in subjective endpoints.

Publication bias

A funnel plot (Figure 4) of the occurrence of adverse events was constructed. It can be seen from the data that most of the points are located in the upper-middle area, and some studies are clustered at the bottom; this may be due to small sample sizes, and publication bias cannot be ruled out.

Discussion

Network meta-analysis (NMA) was employed in this study to systematically evaluate the efficacy and safety of Omalizumab, Mepolizumab,

Benralizumab, Lebrikizumab and Dupilumab for moderate-to-severe EA in children. To the best of our knowledge, this is one of the first NMAs to strictly define the EA phenotype in children and include the currently available biologics. The findings provide an updated evidence base to support personalized treatment decisions, although several limitations warrant consideration.

In terms of therapeutic results, Dupilumab showed a potential trend toward reduced annual exacerbations (RR = 0.34, SUCRA 94.1%), corresponding to a 66% risk reduction-consistent with the 67% reduction reported in the EA cohort of the 2020 LIBERTY ASTHMA EXPEDITION trial [28]. However, because Dupilumab's network node is supported by only a single RCT (n = 175), this elevated SUCRA score is subject to considerable uncertainty. SUCRA values reflect cumulative probability distributions under limited network evidence rather than definitive clinical superiority or magnitude of effect. Direct head-to-head trials are required before concluding superior clinical efficacy. Mechanistically, Dupilumab blocks both IL-4 and IL-13 pathways, which may account for its observed numerical difference over single-target agents [29]. A 2025 post-hoc analysis of VOYAGE data showed that Dupilumab reduced exacerbations by approximately 58% overall, with more pronounced benefits in severe cases (0.41 vs. 1.07) [30]. Another post-hoc analysis in patients with baseline eosinophils ≥ 500 cells/ μ L reported a 67% reduction in severe exacerbations [31]. These post-hoc findings, however, should be interpreted cautiously as they were not pre-specified.

Regarding FEV₁ improvement, among the evaluable biologics, Omalizumab was the sole agent with reportable subgroup data that showed a significant benefit over placebo (SMD = 1.00, 95% CI: 0.21-1.79). Nevertheless, this finding should be interpreted with caution, as previous meta-analyses have reported inconsistent results [32]. Other biologics (such as Dupilumab and Mepolizumab) could not be evaluated in this pooled FEV₁ analysis because primary trials did not report disaggregated FEV₁ changes for the EA subgroup, preventing direct or indirect comparisons. A post-hoc VOYAGE analysis suggested that Dupilumab

might improve ppFEV₁ in children with baseline eosinophils ≥ 500 cells/ μ L (LS mean difference vs. placebo: 7.98 percentage points; 95% CI: 2.17-13.78; P = 0.007) [31]. However, as a post-hoc observation, this finding remains strictly hypothesis-generating and requires confirmation in pre-specified, direct head-to-head trials.

Regarding quality of life, Dupilumab was associated with significant improvements in the VOYAGE trial (LSMD = 0.34 for PAQLQ(S)-IA; 95% CI: 0.16-0.52; P = 0.0002) [27]. Evidence for Omalizumab remains conflicting: some studies reported improvements [17, 19], while Lanier et al. found no significant difference (LSMD = 0.04; P = 0.676) [24]. This discrepancy may reflect differences in patient age, comorbidities, or instrument sensitivity. Nevertheless, a recent systematic review of biologic therapies in pediatric asthma confirmed that all included studies reported statistically significant improvements in HRQoL using validated instruments, reinforcing the clinical relevance of these agents beyond traditional efficacy endpoints [33].

In terms of safety, Mepolizumab was associated with the lowest safety SUCRA value (4.2%) and a significantly higher AE risk than that of Omalizumab, Dupilumab and placebo. Most AEs were mild to moderate, with headache (19%) and injection site reactions (8%) being most common [9]. Omalizumab showed a relatively favorable safety ranking (SUCRA = 87.8%), consistent with a 2023 systematic review [34]. For SAEs, no statistically significant differences were observed across treatments. However, these numerical probabilities reflect relative rank distributions under limited data and should not be interpreted as absolute clinical safety differences. Therefore, these quantitative values and their associated SUCRA rankings (68.6% for Benralizumab) cannot be interpreted as evidence of clinical superiority or safety advantages, and no definitive clinical conclusions should be drawn regarding relative SAE risks.

Compared with previous studies, this NMA has more direct clinical applicability by focusing specifically on the EA phenotype. However, several limitations of this study must be acknowledged. First, some endpoint data (e.g., quality of life, biomarkers) could not be pooled due to

heterogeneous reporting. Second, the evidence network lacks closed loops, meaning no direct head-to-head comparisons were available; indirect estimates may carry bias. Third, heterogeneity in control group definitions and background therapies across studies represents a notable potential source of bias. While major international multicenter trials (e.g., for Dupilumab, Mepolizumab, and large Omalizumab cohorts) defined control groups as placebo plus standard-of-care (SOC) background therapy (evaluating true add-on biological effects), several smaller trials utilized active comparator controls (e.g., budesonide suspension). Differences in baseline controller medication intensity (e.g., ICS dosage or concomitant LABA usage) could alter the control group's baseline event rate and response magnitude, thereby potentially introducing bias into indirect comparisons across different biological agents. Fourth, blinding was difficult in some smaller open-label trials [7, 17-19] due to differing administration routes (e.g., subcutaneous biologic injections vs. inhaled background control medications). While our meta-regression confirmed that administration route did not significantly confound the objective FEV₁ endpoint ($\beta = 0.42$, 95% CI: -0.58-1.42, $P = 0.39$), quantitative regression could not be extended to subjective outcomes such as health-related quality of life or asthma symptom scores due to limited data. Consequently, potential performance bias and expectation effects stemming from unblinding cannot be completely ruled out for these patient-reported subjective measures, and associated quality of life findings should be interpreted with appropriate caution. Fifth, subgroup analyses by BEC threshold or age (< 6 years) could not be performed due to limited data. Sixth, SAEs were rare; the RR of 7.62 for Benralizumab versus placebo should be interpreted with extreme caution, as it arose from zero events in the Benralizumab arm versus few events in the placebo arm [26], resulting in a very wide confidence interval (0.21-273). Seventh, and most importantly, the two main efficacy outcomes were based on only 5 and 6 studies, respectively. Therefore, all findings and comparative rank inferences of this NMA must be regarded as strictly hypothesis-generating rather than conclusive. The SUCRA values presented reflect ranking probabilities only; they should not be equated with absolute differences in clinical

efficacy. Clinicians should prioritize the magnitude of effect estimates and the certainty of evidence over rank order alone [3].

In conclusion, while this network meta-analysis offers updated insights into biologic options for pediatric EA, the findings remain preliminary and hypothesis-generating due to small study counts per node and the total absence of head-to-head data. Clinicians should view these relative rankings as suggestive hypotheses rather than established clinical preferences. Direct, robust head-to-head randomized clinical trials are essential to confirm these hypotheses and establish definitive comparative clinical efficacy in pediatric eosinophilic asthma.

Disclosure of conflict of interest

None.

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Supplementary Table 1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page/Running title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract (page 1)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Section 1 (Introduction), paragraphs 1-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Section 1 (Introduction), final paragraph
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Section 2.1 (Inclusion and Exclusion Criteria)
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Section 2.2 (Literature Review), first paragraph
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Section 2.2 (Literature Review), first paragraph (search string provided)
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Section 2.2 (Literature Review), second paragraph
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Section 2.3 (Data Extraction and Outcome Measures), first paragraph
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Section 2.3 (Data Extraction and Outcome Measures), second paragraph
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Section 2.3 (Data Extraction and Outcome Measures), first paragraph
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Section 2.4 (Assessment of the Study Quality)

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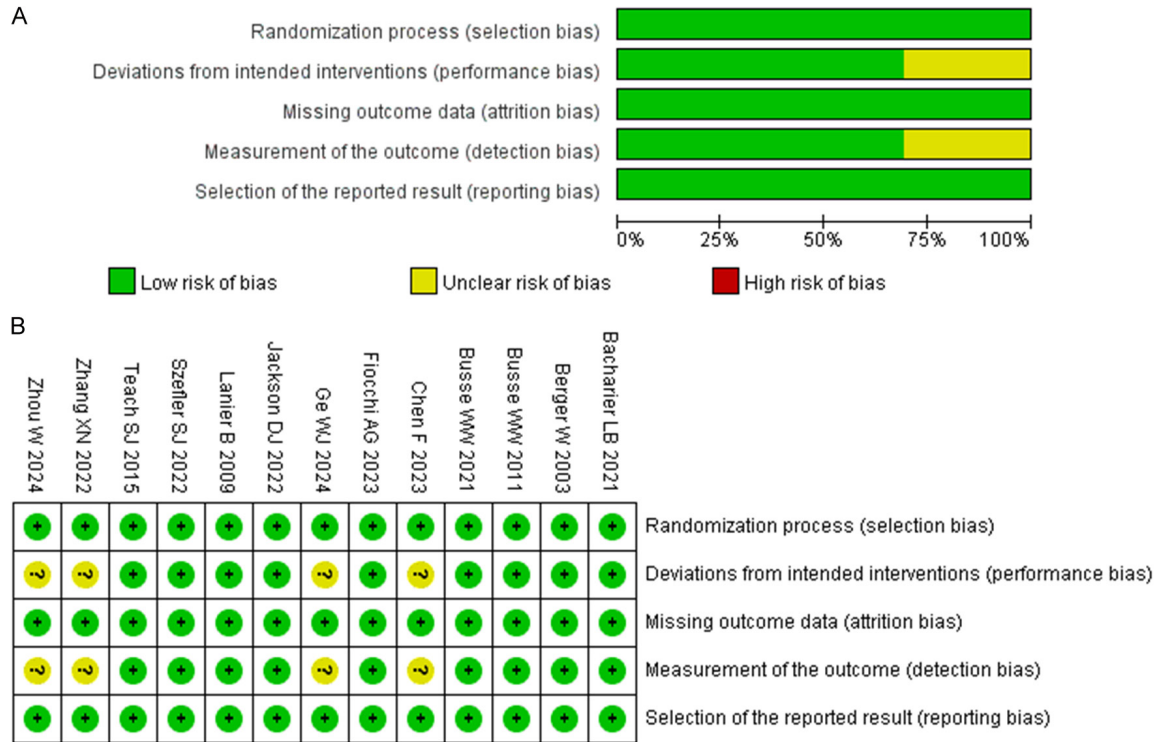
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Section 2.5 (Statistical Analysis), first paragraph
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Section 2.1 (Inclusion and Exclusion Criteria)
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Section 2.3 (Data Extraction and Outcome Measures); Section 2.5 (Statistical Analysis)
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Section 2.5 (Statistical Analysis)
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Section 2.5 (Statistical Analysis)
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Section 2.6 (Sensitivity and Specificity Analysis); Section 3.4.2 (meta-regression for FEV ₁)
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Section 2.6 (Sensitivity and Specificity Analysis); Section 3.4.1(4); Section 3.4.3(4)(5)
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Section 2.5 (Statistical Analysis), final sentence (funnel plot)
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Section 4 (Discussion), limitations subsection
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Section 3.1 (Results of Literature Inclusion); Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Section 3.1 (Results of Literature Inclusion)
Study characteristics	17	Cite each included study and present its characteristics.	Section 3.2 (General features of the included studies); Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Section 3.3 (Assessment of the Risk of Bias); <u>Supplementary Figure 1</u>
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Tables 2-5; Figures 2-4

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Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Section 3.4.1(1), 3.4.2(1), 3.4.3(1), 3.4.4(1)
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Section 3.4.1(2), 3.4.2(2), 3.4.3(2), 3.4.4(2); Tables 2-5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Section 3.4.2(2) (meta-regression); Section 3.4.1(4), 3.4.3(4) (sensitivity analyses)
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Section 3.4.1(4), 3.4.3(4)(5)
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Section 3.5 (Publication Bias); Figure 4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Section 4 (Discussion), limitations subsection
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Section 4 (Discussion), paragraphs 1-6
	23b	Discuss any limitations of the evidence included in the review.	Section 4 (Discussion), limitations subsection
	23c	Discuss any limitations of the review processes used.	Section 4 (Discussion), limitations subsection
	23d	Discuss implications of the results for practice, policy, and future research.	Section 4 (Discussion), final paragraph
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Section 2.1 (Inclusion and Exclusion Criteria), final paragraph
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Section 2.1 (Inclusion and Exclusion Criteria), final paragraph
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Section 2.1 (Inclusion and Exclusion Criteria), final paragraph (retrospective registration disclosed)
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title page/Conflict of Interest statement
Competing interests	26	Declare any competing interests of review authors.	Conflict of Interest statement
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplementary Material (PRISMA-NMA checklist; risk of bias assessment)

Note: From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>.

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Supplementary Figure 1. Outcomes of the bias evaluation process for the enrolled papers. Figure legends: A. “Bias assessment” graph shows the evaluators’ judgments of all bias factors, expressed as the proportion of trials that mentioned that factor in the entire group of enrolled trials. B. “Bias Assessment” Overview: The evaluators’ ratings of each bias factor for all enrolled trials. (+) indicates a low risk of bias; (?) indicates an unknown risk of bias.