APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Efficacy and safety of biologics in children and adolescents with eosinophilic asthma: A systematic review and meta-Analysis

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Abstract

Background: Eosinophilic asthma is a severe phenotype in pediatrics, often refractory to conventional therapy. Biologic agents targeting Type 2 inflammatory pathway are increasingly used in children and adolescents.

Objective: To evaluate the efficacy and safety of omalizumab, mepolizumab, benralizumab, and dupilumab in pediatric eosinophilic asthma.

Methods: We systematically searched eight databases to March 31, 2025 (PROSPERO: CRD420251017602). Eligible studies were randomized controlled or controlled observational trials in patients ≤ 18 years. Outcomes included lung function, asthma control, quality of life (QoL), and adverse events (AEs).

Results: Twenty-two studies (n = 2,468) were included. Biologics significantly improved predicted FEV_1 (SMD = 0.97, 95%CI: 0.38–1.57), asthma control also improved (SMD = 2.84, 95%CI: 1.40–4.28), as did quality of life (SMD = 1.72, 95%CI: 0.39–3.05). Overall AEs were more frequent (OR 1.48, 95%CI 1.22–1.81), but serious AEs were rare and not increased. Evidence was strongest for omalizumab; data for other biologics remain limited.

Conclusion: Biologic therapies are associated with improvements in clinical outcomes in children and adolescents with eosinophilic asthma, with an increased incidence of predominantly mild adverse events. However, the current evidence is largely driven by studies of omalizumab, and data for other biologics remain limited in pediatric populations. Further long-term and comparative studies are warranted to better define the efficacy and safety profiles of individual biologic agents.

Key words: Eosinophilic asthma; children; adolescents; monoclonal antibodies; Type 2 inflammation; meta-analysis

Citation:
Geng, Y., Xu, J. (0000). Efficacy and safety of biologics in children and adolescents with eosinophilic asthma: A systematic review and meta-Analysis.
Asian Pac J Allergy Immunol, 00(0), 000-000.
https://doi.org/10.12932/ap-151025-2164

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Introduction

Asthma is one of the most prevalent chronic respiratory diseases in children and is characterized by significant heterogeneity, with chronic airway inflammation serving as its central pathological feature.[1,2] Although most children respond well to conventional treatments, approximately 5%-10% are classified as having severe asthma,[3] characterized by the need for high-intensity treatments or significant symptoms despite standardized treatment.[4] Although this group is small in proportion among affected children, it represents a significant disease burden and consumes substantial healthcare resources. Among the various inflammatory phenotypes of severe asthma, Type 2 inflammation predominates, particularly eosinophilic inflammation.[5,6] Studies indicate that 50%-90% of patients with severe asthma exhibit eosinophil-mediated features,

including elevated eosinophil counts in blood and airways and activation of cytokines such as IL-5, IL-4, and IL-13.[7-9] This phenotype is common in children and adolescents and oftencoexists with allergic rhinitis and eczema.[8] Eosinophilic asthma typically presents recurrent acute exacerbations, declining lung function, impaired quality of life, and poor response to high doses of inhaled corticosteroids and combined control medications,[4,10] thereby emphasizing the pressing need for more precise and targeted therapeutic approaches.

Eosinophilic asthma represents a major clinical phenotype of asthma driven by the Type 2 inflammatory pathway, particularly in pediatric populations. In recent years, the treatment landscape for severe eosinophilic asthma has undergone a transformative shift with the emergence of biologic therapies targeting key components of the Type 2 inflammatory pathway. Several monoclonal antibodies have been approved for clinical use, including omalizumab (anti-IgE), mepolizumab and benralizumab (anti-IL-5/IL-5Rα),[11] dupilumab (anti-IL-4Rα),[12,13] and tezepelumab (anti-TSLP).[14] By blocking these pathways, biologics reduce exacerbations, improve asthma control and lung function, and in some cases decrease corticosteroid dependence.[8,15,16] Omalizumab has been widely used in children with allergic asthma; mepolizumab and benralizumab deplete eosinophils and reduce attacks;[16,17] dupilumab alleviates airway hyperreactivity and improves lung function;[18] and tezepelumab shows efficacy across varying baseline eosinophil levels.[14]

Although numerous clinical studies have confirmed the efficacy and safety of these biologics in adults and progressively extended to pediatric and adolescent populations, most studies are placebo-controlled and lack direct comparisons between agents, which limits evidence-based treatment selection. Additionally, systematic evidence for children and adolescents with eosinophilic asthma remains limited, with a lack of comprehensive meta-analyses assessing the efficacy and safety of various biologics in this population. Based on these research gaps, this study aims to use systematic review and meta-analysis methods to compile current evidence on the application of four biologics (omalizumab, mepolizumab, benralizumab, and dupilumab) in children and adolescents with eosinophilic asthma, assessing their effects on improving lung function, asthma control, quality of life, and safety, thereby providing a basis for the formulation of individualized clinical treatment strategies. Tezepelumab was also considered in the present review; however, no eligible randomized controlled studies in pediatric eosinophilic asthma were identified.

Methods

Literature search strategy

A comprehensive literature search was conducted according to a predefined protocol, which has been prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251017602. The search strategy encompassed both Chinese and English databases. For Chinese databases, searches were conducted in China National Knowledge Infrastructure (CNKI), Wanfang Data, and VIP Database. English databases included PubMed, Embase, Cochrane Library, and Web of Science. The literature search was performed from database inception through March 31, 2025. Search strategies incorporated both free-text and MeSH terms around concepts such as "asthma," "children," "adolescents," "eosinophils," "biologics," and specific drug names. For instance, an example English search string was: ("omalizumab" OR "mepolizumab" OR "benralizumab" OR "dupilumab" OR "tezepelumab") AND ("child*" OR "pediatric" OR "adolescent") AND ("asthma" OR "eosinophilic asthma"). The Chinese search included combinations of keywords such as "omalizumab (奥马珠单抗)," "mepolizumab (美泊利单抗)," "benralizumab (贝那利珠单抗)," "dupilumab (度普利尤单抗)," "tezepelumab (特泽鲁单抗)," "eosinophil (嗜酸性粒细胞)," and "asthma (哮喘)." Additionally, reference lists from relevant reviews and previously published systematic reviews were manually checked, and grey literature (e.g., conference abstracts) was searched to identify potentially eligible studies comprehensively.

Inclusion and exclusion criteria

Eligible studies had to fulfill all of the following criteria: (1) Participants were pediatric or adolescent patients (defined as < 18 years) diagnosed with eosinophilic asthma, defined as elevated peripheral blood eosinophil counts (commonly ≥ 150–300 cells/μL, depending on study criteria) and/or evidence of airway eosinophilic inflammation, or classified as type 2–high phenotype according to trial definitions; (2) Interventions included one of the five biologics (omalizumab, mepolizumab, benralizumab, dupilumab, or tezepelumab), used alone or in combination with standard asthma therapy. Although tezepelumab was included in the predefined search strategy, no pediatric randomized controlled trials meeting the inclusion criteria were identified and therefore it was not included in the final meta-analysis. Comparators could be placebo plus standard therapy, standard therapy alone, or another biologic; (3) Studies must have reported at least one primary outcome of interest, including annual asthma exacerbation rate (or annual exacerbation frequency) and asthma-related quality of life or asthma control scores; (4) Study designs were randomized controlled trials (RCTs). Exclusion criteria were: (1) case reports, case series, or single-arm studies without control groups; (2) duplicate publications or overlapping datasets (the most recent or complete dataset was selected if multiple reports existed); (3) studies without accessible full texts or studies lacking critical outcome data.

Data extraction and risk of bias assessment

Two researchers independently extracted data using a standardized form. The extracted information included the first author's name, year of publication, country of study, study design, characteristics of the participants, interventions and control measures, follow-up duration,

and primary and secondary outcome measures. The outcomes included forced expiratory volume in one second (FEV_1, % predicted), asthma control score assessed by the Asthma Control Questionnaire (ACQ, unitless score), peak expiratory flow (PEF, liters per second [L/s]), and forced vital capacity (FVC, liters [L]) and quality of life, incidence of adverse events (AEs), and levels of inflammatory biomarkers such as high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6). Any discrepancies were resolved through discussion or by a third researcher's adjudication. For the assessment of risk of bias, RCTs utilized the Cochrane Risk of Bias tool, which evaluates several domains including the randomization process, implementation of interventions, missing data, measurement of outcomes, and selection of reported results.

Statistical Analysis Methods

This study employed R software (version 4.3.2) for meta-analysis and graphical visualization of data. For continuous outcomes such as FEV_1, asthma control scores, and quality of life scores, the standardized mean difference (SMD) along with 95% confidence intervals (CIs) were calculated. For dichotomous outcomes, such as the incidence of adverse events, odds ratios (OR) along with 95% CIs were calculated. Heterogeneity was assessed using Cochran's Q test and the I^2 statistic. If I^2 exceeded 50% or if the *p*-value was significant, a random effects model was employed; Otherwise, a fixed effects model was used. Subgroup analyses were conducted in cases of significant heterogeneity to explore potential sources of variability. Sensitivity analyses were performed using the leave-one-out approach and by limiting the analysis to studies with a low risk of bias to assess the robustness of the results. Publication bias was evaluated by funnel plots and further confirmed with Egger's regression test and Begg's rank correlation test. All visualizations, including forest plots, funnel plots, and sensitivity analysis plots, were generated using R, primarily utilizing the meta, metafor, and dmetar packages. Statistical significance was set at a two-sided *P* value of less than 0.05.

Results

Literature Screening Process

In the initial identification phase, a total of 3,792 records were sourced from various databases: 2,133 from Chinese databases (CNKI, Wanfang Data, and VIP) and 2,925 from English databases (PubMed, Embase, Cochrane Library, and Web of Science). Prior to screening, 1,266 records were excluded: 1,118 for duplication, 33 as ineligible by automated tools, and 115 for other reasons. Subsequent screening of the remaining records resulted in 3,478 being discarded due to irrelevance or incomplete data, leaving 314 reports for detailed evaluation. Of these, three reports were unattainable. During the eligibility assessment, 311 reports were scrutinized, resulting in the exclusion of 109 for focusing on adult subjects, 87 for the absence of a control group, 29 due to inaccessible data, and 64 classified as case reports, letters, or other unsuitable document types (**Figure 1**). Ultimately, 22 studies fulfilled all inclusion criteria and were incorporated into the review.[8,9,11,16,17,19-27]

Characteristics and Risk of Bias Evaluation of Included Literature

This review included 22 RCTs conducted in the USA, Sweden, and China. Each study utilized an RCT design with sample sizes ranging from 32 to 624 participants, addressing asthma severities from mild to severe. The follow-up periods varied from 8 weeks to 52 weeks, with interventions involving various biologics such as Dupilumab, Omalizumab, and Benralizumab. Controls were primarily placebos or standard combination therapies (**Table S1**). For the included studies, we assessed the quality using the Cochrane Collaboration's tool for assessing risk of bias, which generally indicated low risks across domains including random sequence generation, allocation concealment, blinding of participants and outcome assessors, data completeness, selective reporting, and other potential biases (**Table S2**).

Main Outcome Analysis

<u>*Improvement in Lung Function*</u>

This meta-analysis assessed pulmonary function indices reported in the included literature, focusing on the FEV_1 (% predicted). According to **Figure 2**, the SMD showed significant improvements in lung function in the treatment group compared to the control group, with an SMD of 0.97 and a 95%CI from 0.38 to 1.57. The heterogeneity was high (I^2 = 88%), and a random effects model was used for the aggregation of effect sizes, indicating significant statistical differences ($p < 0.01$). Additionally, some studies reported on other pulmonary function parameters such as PEF (L/s), with improvements shown in **Figure 3**. The SMD was 1.39 with a 95%CI of 0.39 to 2.39, and heterogeneity I^2 = 95%, indicating high variability among different studies. Improvements in FVC (L) are summarized in **Supplementary Figure S1**, with a SMD of 1.83 and a 95%CI from 0.89 to 2.76, demonstrating significant enhancements in FVC due to biologic treatment.

<u>*Asthma Control*</u>

In assessing asthma control, six studies reported changes in asthma control scores (such as ACQ) before and after treatment. According to **Figure 4**, the meta-analysis results show that the biologics treatment group exhibited statistically significant improvements in asthma control, with a SMD of 2.84 and a 95% CI ranging from 1.40 to 4.28, indicating significant statistical differences ($p < 0.01$). These results demonstrate that biologics targeting the Type 2 inflammation pathway effectively control asthma symptoms in children and adolescents. The heterogeneity analysis indicated a high degree of variability among studies (I^2 = 97%), hence, a random effects model was used to combine the effect sizes.

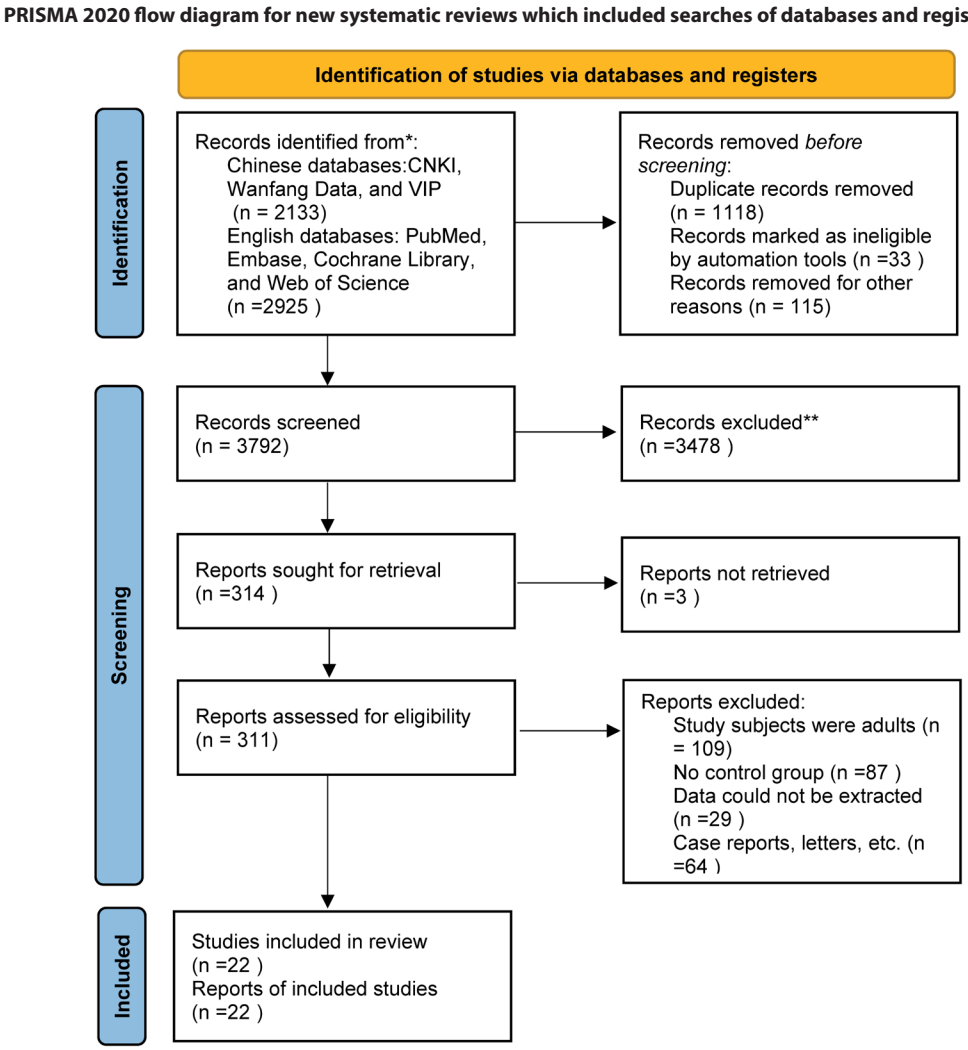

Figure 1. PRISMA Flowchart of Literature Screening Process.

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

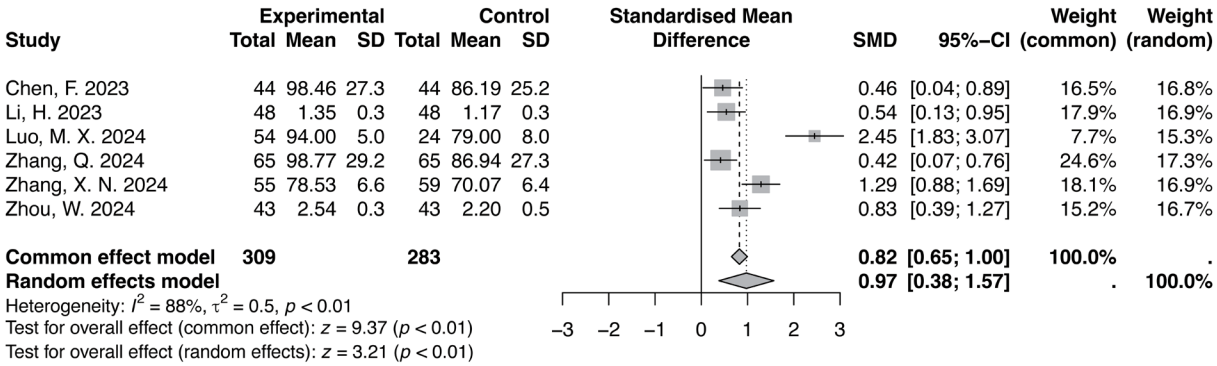

Figure 2. Forest Plot Analysis of Predicted FEV_1 Percentages.

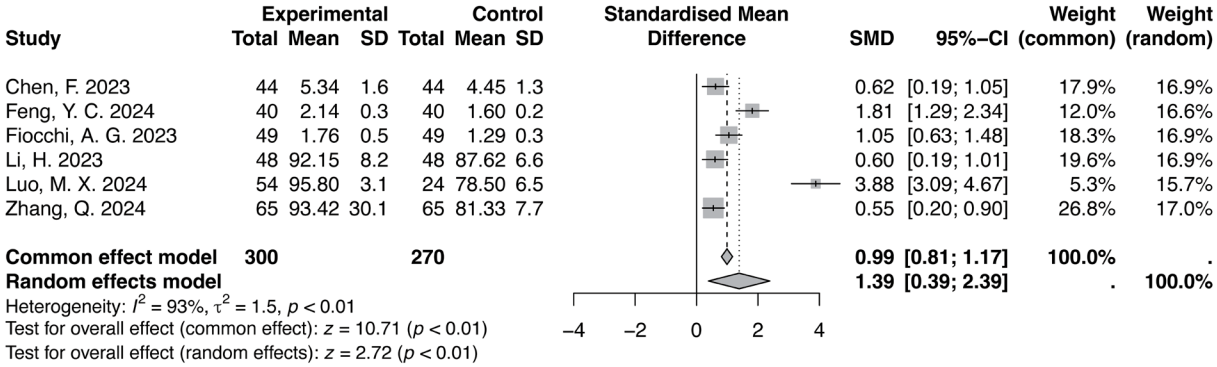

Figure 3. Forest Plot Analysis of Improvements in PEF.

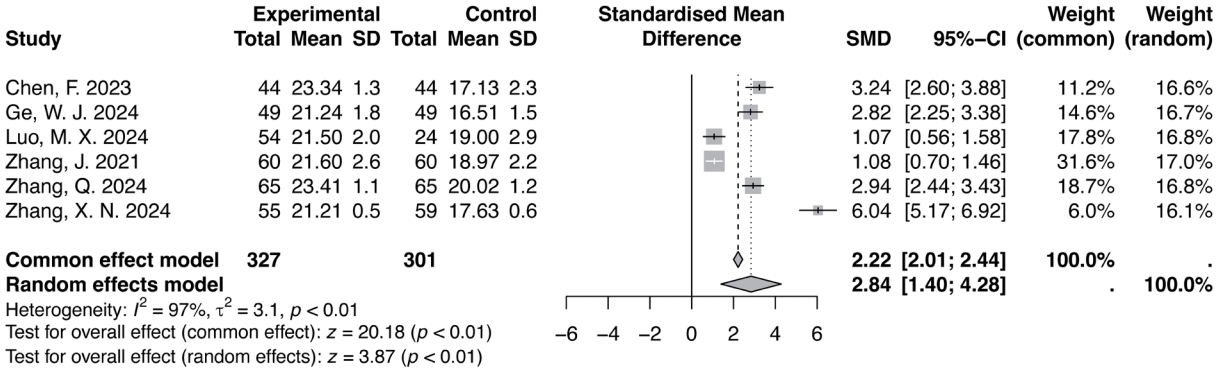

Figure 4. Forest Plot Analysis in Asthma Control Scores.

Improvement in Quality of Life

This study included three research evaluating the impact of biologics on the quality of life in children with asthma, assessed using the PAQLQ. The meta-analysis demonstrated significant improvements in the quality-of-life scores in the treatment group compared to the control group, with a SMD of 1.72, 95% CI from 0.39 to 3.05, p = 0.01 (**Figure 5**). Although these improvements reached the minimum clinically important difference, the evidence is limited by the small number of contributing studies, and the results should be interpreted with caution.

Adverse Event Incidence

This study included 18 research reporting the incidence of adverse events during treatment. The meta-analysis showed no significant difference in the overall incidence of adverse events between the biologic treatment group and the control group, with an overall OR of 1.48, 95% CI from 1.22 to 1.81, p < 0.01 (**Figure 6**), indicating good overall safety of biologics. Most adverse events were mild to moderate, commonly including injection site reactions and upper respiratory infections, with no reports of treatment discontinuation due to serious adverse events.

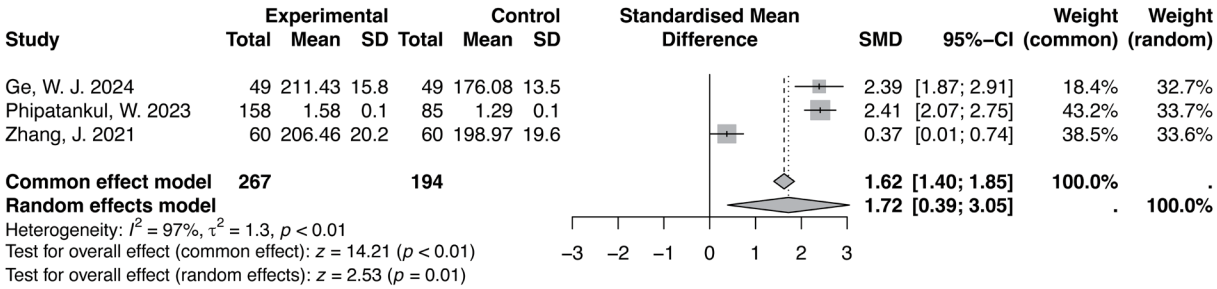

Figure 5. Forest Plot Analysis in quality-of-life scores.

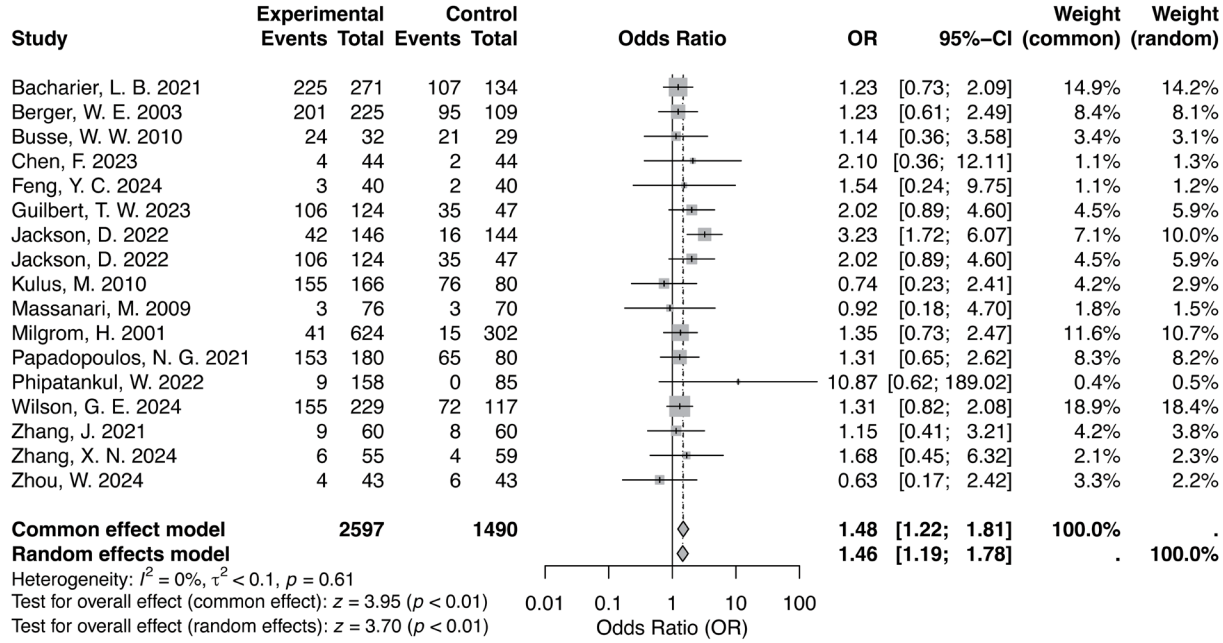

Figure 6. Forest Plot Analysis in Adverse Event Incidence.

Changes in Inflammatory Markers

Several studies reported changes in inflammatory biomarkers before and after treatment, including hs-CRP and IL-6 levels. As shown in **Figure S2**, there was a significant reduction in hs-CRP levels in the treatment group, with a SMD of -1.27, 95% confidence interval from -1.78 to -0.76, $p < 0.01$. Changes in IL-6 levels are illustrated in **Figure S3**, with an SMD of -1.93, 95% confidence interval from -2.44 to -1.42, also showing significant improvement. These results suggest that biologics have biological activity in suppressing systemic or local airway inflammation, which may correlate with improved clinical outcomes.

Sensitivity Analysis and Publication Bias Assessment

Sensitivity Analysis

To verify the robustness of the meta-analysis results, this study performed a leave-one-out sensitivity analysis on the main outcome indicators. The results showed that after the removal of any single study, the changes in the combined effect sizes for lung function (FEV_1 etc.), asthma control scores, quality of life improvements, and adverse event incidence were minimal, with no fundamental changes in overall statistical significance (**Table S3**). This suggests that the meta-analysis results are stable and not influenced by any extreme values from individual studies.

Publication Bias Assessment

When the number of included studies was greater than or equal to ten, the funnel plots demonstrated a fundamentally symmetric distribution, indicating no apparent signs of small-study bias (**Figure S4**). Further quantitative analysis using Egger's linear regression test and Begg's rank correlation test revealed statistically significant publication bias tests for lung function (FEV1%, PEF, FVC) and ACQ, suggesting a lower degree of bias (**Table S4**), thereby enhancing the credibility of these results. For quality of life and adverse event incidence rates, the tests showed non-significant results (**Table S4**), indicating minimal or no publication bias. Results for inflammatory markers (hs-CRP and IL-6) also indicated a low risk of publication bias (**Table S4**), confirming the stability and reliability of these data. Overall, these findings support the scientific validity and objectivity of the meta-analysis results.

Discussion

This study systematically synthesized evidence from 22 randomized controlled trials to evaluate the efficacy and safety of biologic agents targeting the Type 2 inflammatory pathway in children and adolescents with eosinophilic asthma, a major phenotype of type 2 asthma. Eosinophilic inflammation in the pediatric population is often associated with poor response to conventional therapies and a high burden of morbidity. The results of this meta-analysis demonstrated that biologics targeting key mediators, such as IgE, IL-5, IL-4, IL-13, and TSLP—are associated with significant clinical benefits. Notable improvements were observed in pulmonary function parameters, asthma symptom control, and patient-reported quality of life, all of which are critical to optimizing long-term outcomes in this vulnerable age group. These benefits are particularly meaningful given the limitations of standard inhaled corticosteroid-based regimens in severe cases. Furthermore, the safety analysis revealed a low incidence of adverse events, most of which were mild to moderate in nature, with no significant increase compared to control groups. This favorable risk-benefit profile supports the integration of biologic therapies into the management strategy for pediatric eosinophilic asthma, especially in patients who remain symptomatic despite optimal conventional treatment.

Improvements in lung function were particularly notable, with consistent trends observed across studies in predicted FEV_1, PEF, and FVC, likely reflecting the alleviation of airway inflammation following targeted intervention.[11,21,22] Mepolizumab[16,28] and benralizumab,[4,11] by blocking IL-5 or its receptor, effectively suppress the recruitment, survival, and activation of eosinophils. Eosinophils are known to release cytotoxic granules, cytokines, and lipid mediators that contribute to airway wall edema, smooth muscle hypertrophy, mucus hypersecretion, and epithelial barrier dysfunction.[14,16,21] Persistent eosinophilic infiltration is also implicated in airway remodeling processes that lead to irreversible structural changes over time.[19,24,29] Therefore, the ability of these biologics to effectively deplete eosinophils may not only improve short-term pulmonary function but also mitigate long-term airway damage and decline in respiratory capacity. Notably, the improvements in lung function were observed even in patients with poor baseline control, indicating the potential utility of these therapies in more severe pediatric phenotypes.

With respect to symptom control, the significant improvement in ACQ scores indicates a meaningful decrease in both the frequency and severity of asthma exacerbations. This therapeutic benefit likely extends beyond the inhibition of a single inflammatory mediator and may involve broader modulation of immune pathways.[21,25] For instance, dupilumab simultaneously inhibits IL-4 and IL-13 signaling, disrupting the Th2-driven inflammatory response,[14,30] while omalizumab prevents IgE binding to mast cells and basophils, attenuating downstream allergic inflammation,[17,29] which is particularly beneficial for children with coexisting atopic conditions. Although only a few studies reported quality-of-life outcomes, the observed improvements reached clinical significance. In pediatric populations, better symptom control is strongly associated with improved activity tolerance, sleep, and psychosocial well-being, suggesting that biologic therapy may provide functional benefits beyond respiratory outcomes. From a pediatric clinical perspective, outcomes such as asthma exacerbation reduction and corticosteroid-sparing effects are of particular importance, as they are closely associated with disease burden, growth, and long-term safety. Although these outcomes are highly clinically relevant, they were inconsistently reported across the included studies, with substantial variation in definitions and reporting formats, which precluded quantitative synthesis in the present meta-analysis. Nevertheless, the observed improvements in asthma control and lung function may indirectly reflect a reduction in exacerbation risk and treatment burden. Future pediatric studies should prioritize standardized reporting of exacerbation and steroid-sparing outcomes to better inform clinical decision-making.

In terms of safety, current evidence suggests that the five biologics have comparable adverse event rates to those observed in control groups.[8,26,31] Reported events were predominantly mild to moderate severity, such as injection site reactions and upper respiratory tract infections, with no documented cases of treatment discontinuation due to serious adverse effects.[8,26,31] These findings imply that, despite their immunomodulatory nature, biologics are clinically manageable and acceptable in pediatric and adolescent patients. Furthermore, several studies reported significant reductions in inflammation-related biomarkers, including hs-CRP and IL-6,[21,23,32] following treatment. This supports the notion that clinical improvements may be accompanied by meaningful suppression of systemic or local airway inflammation. The reduction in these markers may reflect a broader downregulation of the inflammatory cascade, suggesting that biologics may not only relieve symptoms but also exert a potential disease-modifying effect. Nevertheless, given that most included studies had relatively short follow-up durations, long-term safety data in pediatric populations remain limited and warrant further investigation.

This meta-analysis has several limitations that should be considered when interpreting the findings. First, most included trials evaluated omalizumab, while relatively few investigated mepolizumab, benralizumab, or dupilumab, and no eligible pediatric studies were identified for tezepelumab. As a result, the pooled estimates largely reflect the evidence base for omalizumab, limiting the generalizability to other biologics with different mechanisms of action, dosing regimens, and indications. Second, substantial heterogeneity was observed across major outcomes, likely attributable to differences in eosinophil cut-off values, patient age, baseline asthma severity, biologics used, follow-up duration, and control interventions. Such heterogeneity may weaken the reliability of pooled effect estimates, and the results should therefore be interpreted with caution. Third, most included studies enrolled relatively small pediatric populations and had short to moderate follow-up durations (ranging from 8 to 52 weeks), which limits the assessment of long-term efficacy, safety, and potential disease-modifying effects of biologic therapies in children and adolescents. Fourth, only a small number of studies contributed to the analysis of quality-of-life outcomes, limiting the robustness and generalizability of these findings. Finally, all included studies were placebo-controlled, and no head-to-head comparisons between biologics were available. In addition, real-world pediatric data remain scarce, which may limit the external validity and generalizability of the results to routine clinical practice. Collectively, these limitations highlight the need for larger, longer-term, comparative, and real-world studies to better inform individualized biologic treatment strategies for pediatric eosinophilic asthma.

Conclusion

Current evidence suggests that biologic therapies targeting the type 2 inflammatory pathway are associated with improvements in clinical outcomes in children and adolescents with eosinophilic asthma. However, substantial heterogeneity was observed across studies, and the available evidence is largely driven by trials of omalizumab, while data for other biologic agents remain limited in pediatric populations. These factors should be considered when interpreting the findings. Further long-term, comparative, and agent-specific studies are needed to better define the role of individual biologics in pediatric asthma management.

Acknowledgments

This paper has not received funding support from any foundation.

Declaration of interests

The authors declare no competing interests regarding this publication.

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Supplementary material

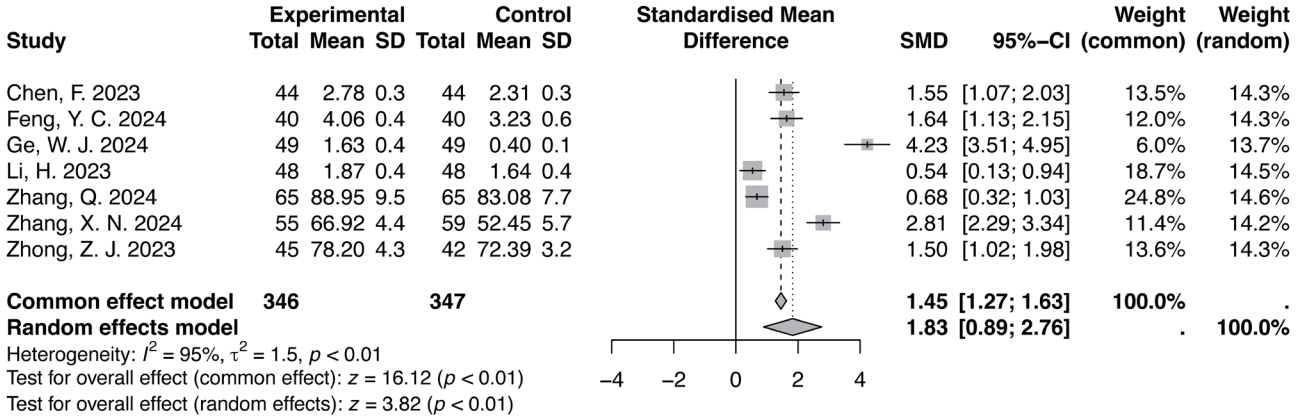

Figure S1. Meta-Analysis of Improvements in FVC (L).

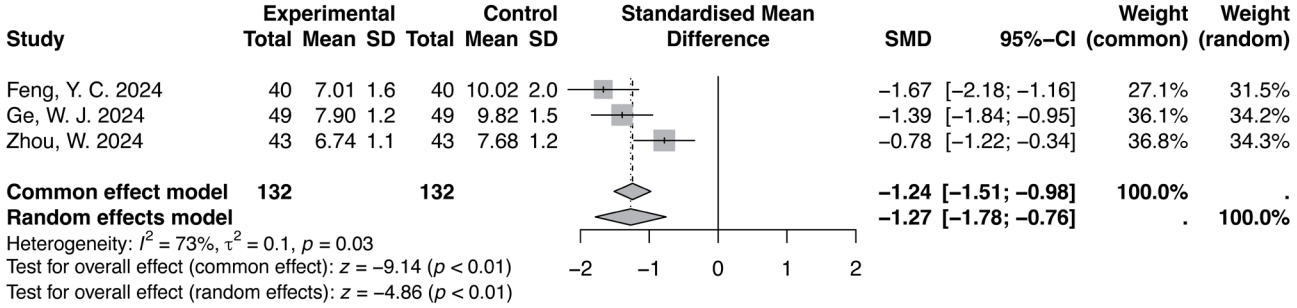

Figure S2. Meta-Analysis of Improvements in hs-CRP Levels.

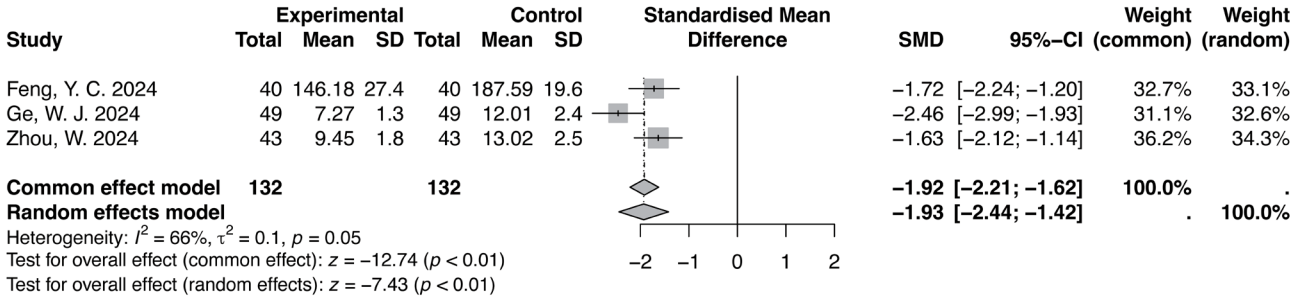

Figure S3. Meta-Analysis of Improvements in IL-6 Levels.

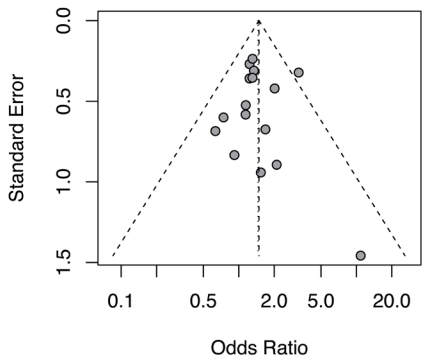

Figure S4. Funnel plots assessing publication bias across included studies.

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Table S1. Characteristics of Included Studies.

study	Year	Region	Study Design	Sample Size (E/C)	Age, years (E/C)	Asthma severity	Follow-up	Intervention / Antibody type	Control
Bacharier, L. B.[1]	2021	USA	RCT	236//114	8.9 ± 1.6//9.0 ± 1.6	Moderate-to-severe asthma	12 weeks	Dupilumab	Placebo
Berger, W. E.[2]	2003	USA	RCT	225//109	< 18	Moderate-to-severe asthma	28 weeks	Omalizumab	Placebo
Busse, W. W.[3]	2010	Sweden	RCT	32//29	15.6 ± 1.39//15.5 ± 1.63	Severe asthma	8 weeks	Benralizumab	Placebo
Chen, F.[4]	2023	China	RCT	44//44	8.52 ± 1.12//8.39 ± 1.03	Moderate-to-severe asthma	12 weeks	Omalizumab	Standard combination therapy
Feng, Y. C.[5]	2024	China	RCT	40//40	8.25 ± 1.21//8.27 ± 1.18	Mild / Moderate / Severe	/	Omalizumab	Standard combination therapy
Ge, W. J.[6]	2024	China	RCT	49//49	6.62 ± 1.25//6.54 ± 1.18	Moderate-to-severe asthma	12 weeks	Omalizumab	Standard combination therapy
Guilbert, T. W.[7]	2023	USA	RCT	124//47	9.2 ± 1.6//8.9 ± 1.5	Moderate-to-severe asthma	52 weeks	Dupilumab	Placebo
Jackson, D.[8]	2022	USA	RCT	146//144	9.0 – 13.0//9.0 – 13.0	Mild / Moderate / Severe	52 weeks	Mepolizumab	Placebo
Jackson, D.[9]	2022	USA	RCT	126//48	8.8 ± 1.6//9.2 ± 1.5	Moderate-to-severe asthma	52 weeks	Dupilumab	Placebo
Kulus, M.[10]	2010	USA	RCT	166//80	9.1 ± 1.71//8.6 ± 1.74	Severe asthma	52 weeks	Omalizumab	Placebo
Li, H.[11]	2023	China	RCT	48//48	9.94 ± 1.84//9.94 ± 1.84	Mild / Moderate / Severe	/	Omalizumab	Standard combination therapy
Luo, M. X.[12]	2024	China	RCT	54//24	8.5 ± 1.6//8.0 ± 1.6	Moderate-to-severe asthma	8 weeks	Omalizumab	Standard combination therapy
Maspero, J. F.[13]	2023	USA	RCT	76//70	14.2 ± 1.72//14.2 ± 1.64	Moderate-to-severe asthma	28 weeks	Omalizumab	Standard combination therapy
Nakamura, M.[14]	2021	USA	RCT	624//302	< 18	Moderate-to-severe asthma	52 weeks	Omalizumab	Placebo
Papadopoulos, N. G.[15]	2021	USA	RCT	180//80	< 18	Moderate-to-severe asthma	52 weeks	Dupilumab	Placebo
Phipatankul, W.[16]	2023	USA	RCT	158//85	< 18	Moderate-to-severe asthma	52 weeks	Dupilumab	Placebo
Szefler, S. J.[17]	2022	USA	RCT	229//117	14.2 ± 1.62//14.2 ± 1.5	Mild / Moderate / Severe	52 weeks	Lebrikizumab	Placebo
Zhang, J.[18]	2021	China	RCT	60//60	7.03 ± 0.84//7.04 ± 0.29	Severe asthma	16 weeks	Omalizumab	Standard combination therapy
Zhang, Q.[19]	2024	China	RCT	65//65	9.14 ± 1.52//9.43 ± 1.45	Moderate-to-severe asthma	16 weeks	Omalizumab	Standard combination therapy
Zhang, X. N.[20]	2024	China	RCT	55//59	14.23 ± 1.22//14.45 ± 1.27	Severe asthma	24 weeks	Omalizumab	Standard combination therapy
Zhong, Z. J.[21]	2023	China	RCT	42//42	10.60 ± 1.86//10.30 ± 2.24	Severe asthma	24 weeks	Omalizumab	Standard combination therapy
Zhou, W.[22]	2024	China	RCT	43//43	5.94 ± 1.31//5.68 ± 1.38	Severe asthma	16 weeks	Omalizumab	Standard combination therapy

Table S2. Risk of Bias Assessment of Included Studies.

Study	Year	Random Sequence	Allocation Concealment	Blinding Participants	Blinding Outcome	Incomplete Data	Selective Reporting	Other Bias	Overall Risk
Bacharier, L. B.	2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Berger, W. E.	2003	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns
Busse, W. W.	2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chen, F.	2023	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Some concerns
Feng, Y. C.	2023	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Some concerns
Ge, W. J.	2024	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Some concerns
Guilbert, T. W.	2024	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jackson, D.	2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jackson, D.	2024	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kulus, M.	2010	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Some concerns
Li, H.	2024	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Some concerns
Luo, M. X.	2023	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Some concerns
Maspero, J. F.	2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nakamura, M.	2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Papadopoulos, N. G.	2023	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Phipatankul, W.	2023	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Szefler, S. J.	2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zhang, J.	2023	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Some concerns
Zhang, Q.	2021	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Some concerns
Zhang, X. N.	2022	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Some concerns
Zhong, Z. J.	2022	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Some concerns
Zhou, W.	2024	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Some concerns

Table S3. Sensitivity Analysis Results.

	SMD/OR	95%CI	*p*-value	tau^2	tau	I^2
FEV1 (%)	0.97	0.38-1.57	< 0.01	0.50	0.71	88%
PEF (L/s)	1.39	0.39-2.39	< 0.01	1.50	1.22	93%
FVC (L)	1.83	0.89-2.76	< 0.01	1.53	1.24	95%
ACQ	2.84	1.40-4.28	< 0.01	3.14	1.77	97%
Quality-of-life scores	1.72	0.39-3.05	0.01	1.33	1.16	97%
Adverse Event Incidence	1.48	1.22-1.81	< 0.01	0.01	0.02	0%
hs-CRP (mg/mL)	-1.27	-1.76-0.76	< 0.01	0.15	0.39	73%
IL-6 (pg/mL)	-1.93	-1.02	< 0.01	0.13	0.37	66%

Table S4. Results of Egger's and Begg's Tests for Publication Bias.

Outcomes	Egger's test		Begg's test	
	t	*p*-value	z	*p*-value
FEV1 (%)	2.98	0.04	1.32	0.19
PEF (L/s)	7.24	0.01	2.44	0.01
FVC (L)	5.81	0.02	3.15	0.01
ACQ	3.87	0.02	2.07	0.04
Quality-of-life scores	0.25	0.45	-0.52	0.60
Adverse Event Incidence	0.12	0.81	0.45	0.65
hs-CRP (mg/mL)	-1.11	0.47	-1.57	0.12
IL-6 (pg/mL)	-1.42	0.39	-1.57	0.12

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