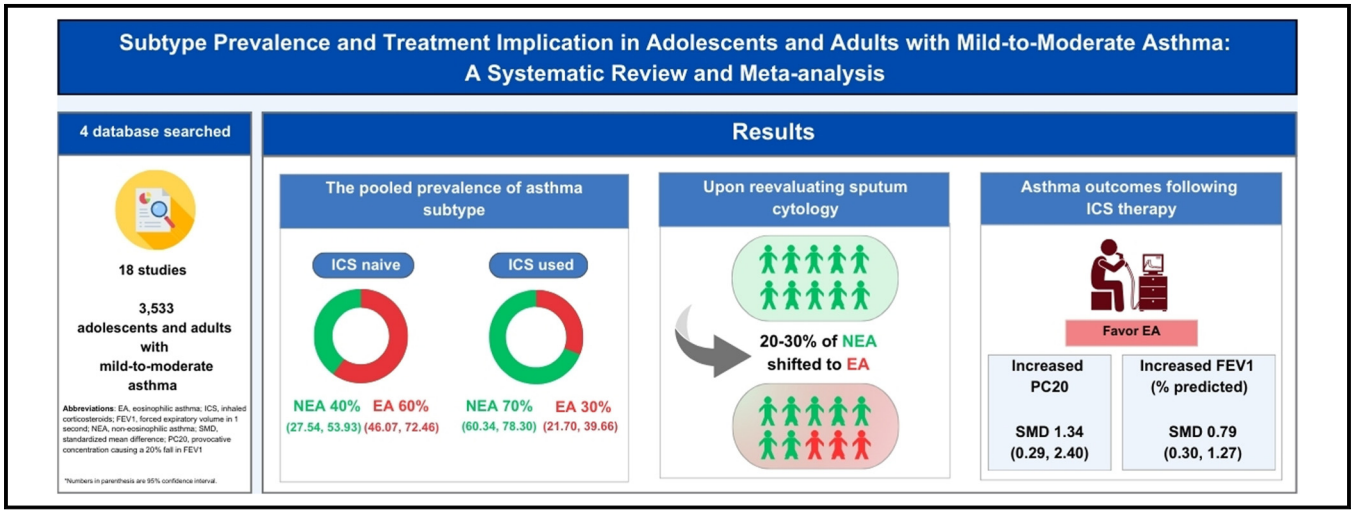
Subtype prevalence and treatment implication in adolescents and adults with mild-to-moderate asthma: Systematic review and meta-analysis

Chamard Wongsa, MD,[a] Pakpoom Wongyikul, MD,[b,d] Piyaporn Chokevittaya, MD,[a] Anapat Nititammaluk, MD,[a] Kay Khine Soe, MD, PhD,[c] Phichayut Phinyo, MD, PhD,[b,d,e] Jonathan A. Bernstein, MD,[f] and Torpong Thongngarm, MD[a]

Bangkok and Chiang Mai, Thailand; Melaka, Malaysia; and Cincinnati, Ohio

GRAPHICAL ABSTRACT



Background: Inhaled corticosteroid (ICS)-containing regimens are the mainstay for treating asthma despite usually being ineffective in noneosinophilic asthma (NEA). Data on the prevalence of NEA versus eosinophilic asthma (EA) in mild-to-moderate asthma are limited.

Objective: We performed a systematic review of the prevalence of mild-to-moderate asthma in adolescents and adults using sputum inflammatory cell analysis and their responses to ICS.

Methods: We searched electronic databases (PubMed, Scopus, EMBASE, Cochrane) for studies in adolescents and adults with mild-to-moderate asthma. The primary outcome was the prevalence of asthma subtypes based on sputum inflammatory cell analysis, categorized into EA and NEA. The secondary outcome involved comparing asthma outcomes between different subtypes after ICS therapy. Certainty of evidence was reported for each pooled analysis.

Results: Eighteen studies involving 3,533 adolescents and adults with mild-to-moderate asthma were reviewed. The pooled prevalence (95% confidence interval) of NEA was estimated at 40.39% (27.54, 53.93) in patients with ICS naive with very low certainty of evidence. On reevaluating sputum cytology, the disease of approximately 20% to 30% of patients initially diagnosed as NEA transitioned to the EA subtype. EA patients showed significant improvements in asthma symptoms after ICS therapy: forced expiratory volume in 1 second (standardized mean difference, 0.79; 95% confidence interval, 0.30, 1.27), and airway hyperresponsiveness (standardized mean difference, 1.34; 95% confidence interval, 0.29, 2.40). NEA patients exhibited limited response.

Conclusion: A high proportion of adolescents and adults with mild-to-moderate asthma were identified with NEA subtype disease, which exhibited a poor response to ICS. A thorough

From [a]the Division of Allergy and Clinical Immunology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok; [b]the Center for Clinical Epidemiology and Clinical Statistics, Faculty of Medicine, Chiang Mai University, Chiang Mai; [c]the Department of Pharmacology, Faculty of Medicine, Manipal University College Malaysia, Melaka; [d]the Department of Biomedical Informatics and Clinical Epidemiology (BioCE), Faculty of Medicine, Chiang Mai University, Chiang Mai; [e]Musculoskeletal Science and Translational Research (MSTR), Chiang Mai University, Chiang Mai; and [f]the Division of Rheumatology, Allergy and Immunology, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati.

The first 2 authors contributed equally to this article, and both should be considered first author.

Received for publication July 19, 2024; revised September 9, 2024; accepted for publication September 12, 2024.

Available online November 4, 2024.

Corresponding author: Torpong Thongngarm, MD, Division of Allergy and Clinical Immunology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Rd, Bangkok Noi, Bangkok 10700, Thailand. E-mail: torallergy@gmail.com.

2772-8293

https://doi.org/10.1016/j.jacig.2024.100366

diagnostic evaluation before initiating treatment should be integrated into clinical practice.
Registered in PROSPERO (CRD42023484334) (J Allergy Clin Immunol Global 2025;4:100366.)

Key words: *Asthma, corticosteroid, efficacy, eosinophilic, glucocorticoid, meta-analysis, noneosinophilic, prevalence, subtypes, systematic review*

Mild asthma is defined as being well controlled with steps 1 and 2, while moderate asthma needs step 3 treatment according to the Global Initiative for Asthma (aka GINA) guideline.[1] The recommended therapy for steps 1 to 3 relies on inhaled corticosteroid (ICS)-based regimens, including ICS monotherapy, ICS-formoterol, and ICS–long-acting β_2 agonists.[1] These treatment regimens are generally initiated according to disease severity characterized by symptoms, history of exacerbation, and lung function rather than routinely evaluating asthma subtypes.

Sputum cytology is a tool to assess airway inflammation in asthma by classifying it into eosinophilic, neutrophilic, mixed granulocytic (increased number of both eosinophils and neutrophils), and paucigranulocytic (decreased number of both eosinophils and neutrophils) subtypes.[2,3] The 2 most common subtypes were paucigranulocytic and eosinophilic, with a prevalence in 2 large studies of 40% to 52% and 38% to 42%, while mixed granulocytic and neutrophilic were 3% to 5% and 4% to 15%, respectively.[4,5] These findings emphasized a significant prevalence of the noneosinophilic subtype, observed in certain asthma patients on multiple assessments of sputum cytology on various occasions.[6]

The disease of individuals with eosinophilic asthma (EA) typically exhibits favorable responses to ICS, whereas non-EA (NEA) disease often demonstrates limited responses.[7,8] However, a small randomized placebo-controlled study reported that ICS was also effective in mildly uncontrolled NEA.[9] Consequently, various asthma subtypes that potentially differ in their airway immunopathology need diverse therapeutic interventions. The use of ICS as "a one size fits all" treatment approach in some asthma subtypes may yield minimal clinical benefit and increase overall health care resource utilization. Furthermore, ICS administered in patients with NEA may modify the microbial composition and increase airway bacterial load.[10]

We conducted a systematic review and meta-analysis to assess the subtype prevalence of adolescents and adults with mild-to-moderate asthma stratified by sputum cytology. Additional objectives were to evaluate asthma outcomes of each subtype after ICS treatment.

METHODS

This systematic review and meta-analysis followed the Cochrane Handbook for Systematic Reviews of Intervention and reported in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[11,12] The review protocol was registered in PROSPERO (CRD42023484334).

Data sources and search strategy

A predefined search strategy comprehensively gathered relevant literature, covering inception dates to December 2023 across databases, including PubMed/MEDLINE, Scopus, EMBASE, and the Cochrane Central Register of Controlled Trials. We used specific keywords and controlled vocabulary terms for each database (eg, MeSH headings for PubMed and EMTREE for EMBASE), as shown in Tables E1 to E4 in this article's Online Repository available at www.jaci-global.org. In addition, we reviewed references from prior systematic reviews and meta-analyses on this topic. Any pertinent studies identified during reference reviews but missed in the electronic database searches were also included.

Abbreviations used

AHR:	Airway hyperresponsiveness
BEC:	Blood eosinophil counts
CI:	Confidence interval
EA:	Eosinophilic asthma
FENO:	Fractional exhaled nitric oxide
FEV_1:	Forced expiratory volume in 1 second
GRADE:	Grading of Recommendations, Assessment, Development, and Evaluation
ICS:	Inhaled corticosteroids
NEA:	Non-EA
PC_{20}:	Provocative concentration causing 20% decrease in FEV_1
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-analysis
SMD:	Standardized mean difference

Study selection and outcomes

Any randomized controlled trials, cohort, or cross-sectional studies that fulfilled the following criteria were included in this review: (1) studies involving adolescents and/or adults, 12 years of age or older, with mild-to-moderate asthma, (2) studies reporting data that can be used to estimate the subtype prevalence of the enrolled asthma patients stratified by sputum inflammatory cell types (mandatory, for our primary objective), and (3) studies reporting data concerning the efficacy of ICS compared to placebo or no intervention (optional, for our secondary objective). Exclusion criteria were studies with no abstract, no available full text, or duplicated studies.

The primary outcome was the prevalence of mild-to-moderate asthma subtypes among adolescents and adults, categorized by sputum inflammatory cells in EA and NEA. The percentages and 95% confidence intervals (CIs) of each subtype prevalence were estimated. Additional outcomes were the treatment responses measured by the changes in asthma symptoms, lung function measured by forced expiratory volume in 1 second (FEV_1), and airway hyperresponsiveness (AHR) measured by provocative concentration causing a 20% decrease in FEV_1 (PC_{20}) of each mild-to-moderate asthma subtype.

Screening

After eliminating duplicate studies, 2 investigators (C.W. and A.N.) independently screened records using ASReview (Utrecht University, Utrecht, Netherlands), the open-source machine-learning model for prioritizing relevant records.[13] A sample of both relevant and irrelevant records was included for model training. The model then ranked all records by their relevance to the review topics, from most to least relevant. Previous reports

concerning ASReview's performance indicated that screening approximately 33% of the total records resulted in very few missed eligible studies.[13-15] Therefore, on the basis of prespecified author consensus, our 2 reviewers reasonably extended the screening to up to 50% of the records to ensure comprehensive coverage of eligible studies. Any disagreements that occurred during screening were resolved by consulting the corresponding author.

Data extraction

Two investigators (C.W. and P.C.) independently extracted data from included studies with regard to study authorship, year of publication, study period, country/location, language, study design, inclusion and exclusion criteria, population type (ie, children and/or adults), patient demographics including age and sex, potential effect modifiers (eg, the severity of the disease), number of patients in each subtype, primary outcome, treatment response, and study conclusion. Any discrepancy during the data extraction was resolved through discussion with the corresponding author.

Risk of bias assessment

For the primary objective, 2 authors (K.S. and P.W.) independently evaluated the methodological quality of the included studies. The risk of bias of included studies was evaluated using a tool specifically modified for prevalence studies.[16,17] The following 7 domains were assessed:

1. National population representativeness.
2. Adequacy of sampling frame.
3. Likelihood of selection bias.
4. Likelihood of nonresponse bias.
5. Acceptability of outcome definition.
6. Appropriateness of data collection methods.
7. Adequacy of study period.

Each domain was rated as low or high risk (including those with unclear information).

For the secondary objective, 2 authors (K.S. and P.W.) independently evaluated the quality of each included study using the Newcastle-Ottawa Scale quality assessment tool.[18] Any disagreement was resolved by consulting with a clinical epidemiologist (P.P.) and a clinical allergist (T.T.).

Data synthesis and analysis

All analyses were conducted by Stata 17 (StataCorp), and $P < .05$ was considered statistically significant. For the primary objective, the prevalence of NEA subtype in mild-to-moderate asthma patients receiving and not receiving ICS (ICS naive or mixed ICS naive and ICS withdrawal), along with their corresponding 95% CIs, were estimated by random-effects meta-analysis via the 'metaprop' command in Stata.[17] The statistical heterogeneity of the pooled effect was assessed by the Cochrane Q test and the I^2 statistic. I^2 statistic values of more than 75% indicated significant statistical heterogeneity.[19]

For the secondary objective, if feasible, the pooled differences in ICS treatment responses among patients in each subtype were performed using DerSimonian-Laird random-effects meta-analysis. We estimated the pooled odds ratio or standardized mean difference (SMD), depending on outcome type. A treatment effect with a SMD of 0.2, 0.5, and 0.8 thresholds was considered a small, medium, and large effect, respectively.[20] A leave-one-out sensitivity analysis was conducted to examine the robustness of the main result.

The Egger test was used to assess for publication bias, and $P < .05$ indicated significant publication bias. Assessment of publication bias was carried out when the number of studies equaled or exceeded 10.

Certainty of evidence

Two investigators (K.S. and P.W.) independently evaluated the quality of evidence regarding the pooled differences in ICS responses using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).[21] There were 4 levels of evidence certainty: high, moderate, low, or very low. The quality of evidence depends on the study design, risk of bias, consistency, directness, and precision of the findings.

RESULTS

Search result

A total of 4,653 records were identified from 4 databases. After removing duplicates and screening records, 18 studies involving 3,533 adolescents and adults with mild-to-moderate asthma were included in this systematic review. The PRISMA flow diagram is shown in Fig 1.

Characteristics of included studies

The included studies varied in design, encompassing 1 double-blind crossover study,[22] 4 randomized double-blind studies,[23-26] 9 prospective cohort studies,[8,27-34] and 4 cross-sectional studies.[35-38] The prevalence of asthma subtype was documented across 10 studies for individuals not receiving ICS,[8,22-24,32-37] 3 for those prescribed ICS,[25,26,38] and 5 encompassing both ICS receipt and nonreceipt.[27-31] The summary of characteristics and asthma subtype prevalence in included studies involving patients with mild-to-moderate asthma not receiving ICS are presented in Table I. The most common cutoff for classifying sputum eosinophilia in included studies was ≥3%,[23,25,26,31,33-36,38] followed by ≥2%.[22,27-30,37] The comparison of asthma outcomes between EA and NEA after treatment with ICS is summarized in Table II. Table E5 in the Online Repository available at www.jaci-global.org summarizes the studies' inclusion and exclusion criteria, as well as clinical features and other factors that may affect asthma subtypes. Regarding the inclusion criteria, asthma was diagnosed on the basis of the presence of chronic respiratory symptoms and consistent pulmonary function tests, with or without the AHR test. Some studies included current smokers and individuals with a history of long-term smoking,[24,25,31,35-38] Four of 18 studies reassessed sputum cytology, while the remaining studies performed sputum cytology only once.[28-31]

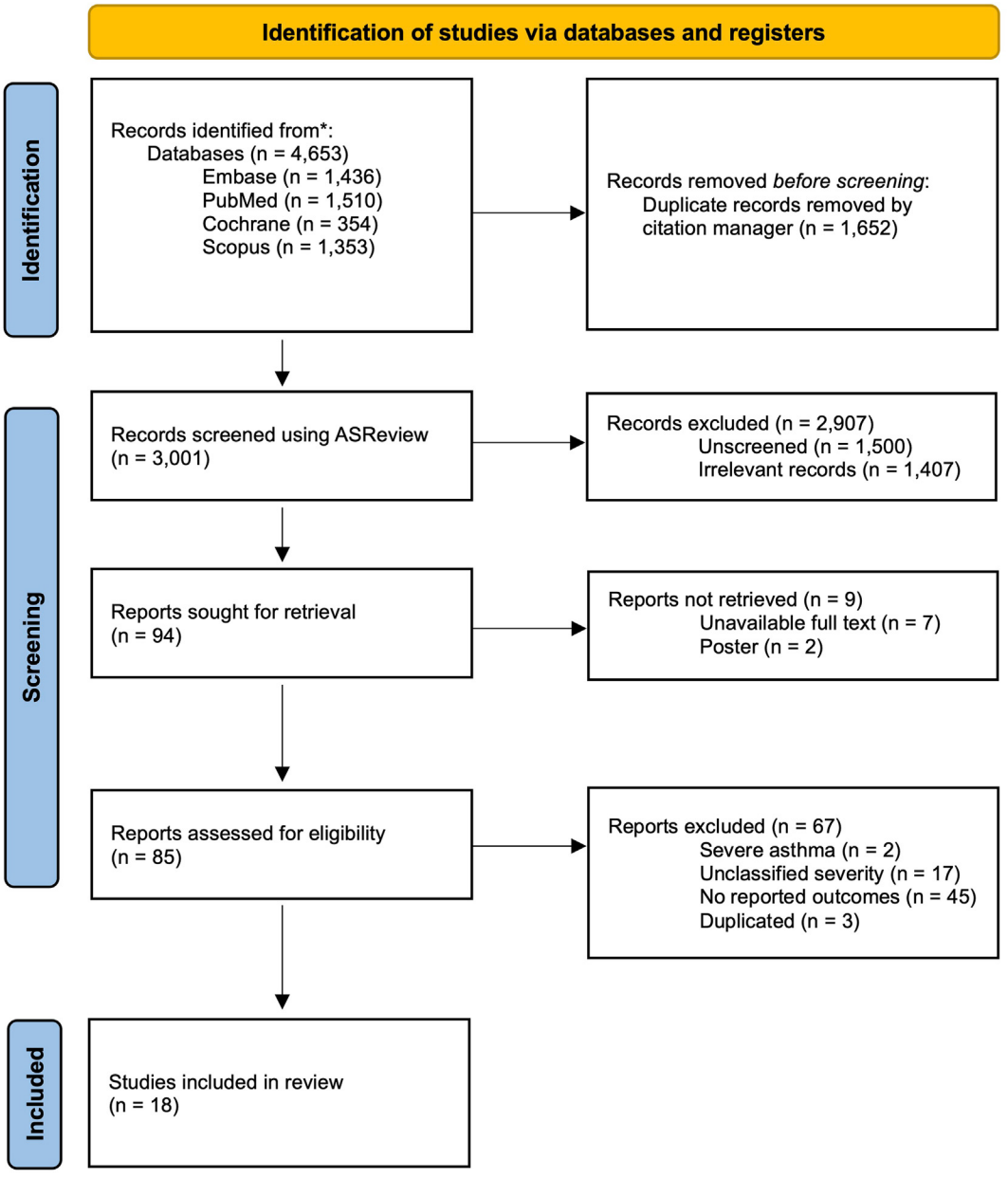


FIG 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) flow diagram of included and excluded studies.

Risk of bias assessment of included studies focusing on subtype prevalence

Fig 2 and Fig E1 in the Online Repository available at www.jaci-global.org summarize the assessment of the risk of bias in individual studies. Most studies had a low risk of bias relative to the study population's being representative of the target population, consecutive or random sampling, nonresponse bias, outcome definition, consistency of data collection, and prevalence period. However, more than half of the included studies had a high risk of bias specific to the study population's being representative of the national population.

Prevalence of NEA subtype in patients not receiving ICS therapy

Eight studies[8,23,24,27,31-34] involving 668 patients with ICS naive and 7 studies[22,28-30,35-37] involving 1,066 patients with mixed ICS naive and ICS withdrawal assessed asthma subtype prevalence. The duration of the ICS withdrawal period ranged from 2 to 12 weeks. The estimated pooled prevalence (95% CI) of NEA in patients with ICS naive was 40.39% (27.54, 53.93), and in those with mixed ICS naive and ICS withdrawal, it was 46.96% (32.62, 61.56), as shown in Fig 3, *A* and *B*.

TABLE I. Characteristics of included studies in mild-to-moderate asthma patients not receiving ICS at time of sputum cytology

Study	Year	Study type (no. of participants)	Age (years)	Asthma severity	Baseline FEV_1 (% predicted)	Previous ICS receipt	Cutoff for sputum eosinophilia	Prevalence (no.)	
								EA	NEA
Mirsadraee[23]	2021	Randomized, double blind (52)	44.6 ± 18.5	Moderate	69.3 ± 5.4	ICS naive	≥3%	44 (23)	56 (29)
Lazarus[22]	2019	Double blind, crossover (366)	EA 31.1 ± 14.2; NEA 31.2 ± 13.8	Mild	EA 89.5 ± 10.8; NEA 92.7 ± 12.4	ICS naive or withdrawal ICS at least 3 wk	≥2%	25 (74)	75 (221)
Nyenhuis[27]	2017	Prospective cohort (298)	31.9 ± 10.0*	Mild to moderate	85.5 ± 13.2*	ICS naive	≥2%	36 (106)	64 (192)
Górska[35]	2017	Cross-sectional (24)	51 (31.0-60.5)†	Mild to moderate	88.5 (75.5-97)†	ICS naive or withdrawal ICS at least 6 wk	≥3%	54 (13)	21 (5)
Obase[36]	2016	Cross-sectional (78)	41.7, 48.5§	Mild to moderate	100, 106§	ICS naive or withdrawal ICS at least 2 wk	≥3%	58 (45)	42 (33)
Cianchetti[37]	2014	Cross-sectional (129)	37.8 ± 15.0	Mild to moderate	89.9 ± 15.2	ICS naive or withdrawal ICS at least 12 wk	>2%	65 (84)	35 (45)
McGrath[28]	2012	Multicenter, prospective cohort (350)	30 (25-38)†	Mild to moderate	83.8 ± 13.3	ICS naive or withdrawal ICS at least 2 wk	≥2%	36 (126)	64 (224)
Hancox[29]	2012	Prospective cohort (25)	39.5 ± 11.8	Mild to moderate	NR	ICS naive or withdrawal ICS at least 4 wk	≥2%	68 (17)	32 (8)
Cowan[30]	2010	Prospective cohort (94)	43.0 ± 13.0	Mild to moderate	88.0 ± 16.0	Withdrawal ICS until loss of asthma control or 28 d	≥2%	67 (63)	33 (31)
Bacci[31]	2006	Prospective cohort (67)	EA 32.0 ± 11.0; NEA 45.0 ± 15.0	Moderate	EA 87.9 ± 15.4; NEA 90.2 ± 17.3	ICS naive	≥3%	75 (50)	25 (17)
Jayaram[24]	2005	Randomized, placebo controlled (88)	34.7 ± 10.7*	Mild	75.9 ± 17.7*	ICS naive	≥3.5%	57 (50)	43 (38)
Basyigit[32]	2004	Prospective cohort (45)	EA 56.3 ± 15.0; NEA 54.0 ± 11.5	Moderate	EA 75.6 ± 22.4; NEA 73.4 ± 16.4	ICS naive	≥5%	73 (33)	27 (12)
Green[8]	2002	Prospective cohort (49)	EA 45.0 ± 22.0; NEA 57.0 ± 21.0	Mild	EA 89.0 ± 2.4; NEA 82.0 ± 5.7	ICS naive	>1.9%	78 (38)	22 (11)
Godon[33]	2002	Prospective cohort (46)	EA 30.7 ± 11.0; NEA 34.3 ± 11.6	Mild	EA 80.4 ± 15.5; NEA 79.6 ± 22.3	ICS naive	≥1%	74 (34)	26 (12)
							≥3%	54 (25)	46 (21)
Pavord[34]	1999	Prospective cohort (23)	EA 53.0; NEA 45.0	Mild	EA 86.2; NEA 81.3	ICS naive	≥3%	61 (14)	39 (9)

Data are presented as means ± SDs unless otherwise indicated.
NR, Not reported.
*Overall means and SDs were calculated from reported subgroup via Jamie Decoster method.
†Median (interquartile 25, 75).
§95% CI

Prevalence of NEA subtype in patients receiving ICS

Eight studies encompassing 2,109 patients with mild-to-moderate asthma receiving ICS assessed the asthma subtype prevalence (see Table E6 in the Online Repository available at www.jaci-global.org).[25-31,38] ICS dosages varied, with 2 studies[26,28] using low dose, 3 studies[27,29,38] using medium dose, and 3 studies[25,30,31] using high dose. The estimated pooled prevalence of NEA was 69.68% (95% CI, 60.34, 78.30) (see Fig E2 in the Online Repository).

The analysis of sputum inflammatory cells in 4 studies[23,27,29,30] subcategorized mild-to-moderate asthma into EA, neutrophilic asthma, mixed granulocytic asthma,

TABLE II. Clinical characteristics and asthma outcomes compared between EA and NEA after receiving ICS

Study	Year	Asthma subtype after receiving ICS		ICS receipt and duration	Outcomes after receiving ICS		
		EA	NEA		Symptoms	FEV_1 (% predicted)	AHR
McGrath[28]	2012	22 (109)	78 (377)	Beclomethasone 160 μg/d *or* triamcinolone 800 μg/d for 4-6 wk	EA: significant improvement in asthma symptoms and FEV_1; NEA: no significant improvement		NR
Cowan[30]	2010	42 (37)	58 (51)	Fluticasone propionate 1000 μg/d for 28 days	ACQ, ACT, and AQLQ were significantly improved in EA than NEA	EA ● Before 2.2 ± 0.8 L ● After 2.9 ± 0.8 L ● Δ 34.0 ± 26.0% NEA ● Before 2.7 ± 0.9 L ● After 2.9 ± 0.9 L ● Δ 7.0 ± 7.0%	EA (PC_{20},* mg/mL) ● Before 10.2 (6.0, 17.4)† ● After 141.9 (80.9, 248.9)† ● Doubling dose Δ 3.8 ± 3.0 NEA ● Before 53.9 (26.9, 108.0)† ● After 188.5 (90.3, 393.7)† ● Doubling dose Δ 1.8 ± 2.2
Godon[33]	2002	NR	NR	Fluticasone propionate 250 μg twice daily for 1 mo	Symptom score, β_2-agonist provided, and quality of life improved in both EA and NEA	EA ● Before 77.3 ± 14.8 ● After 88.6 ± 13.2 ● Δ 11.3 (7.4, 15.3)† NEA ● Before 83.5 ± 21.1 ● After 90.4 ± 19.5 ● Δ 6.9 (1.2, 12.5)†	EA (PC_{20},‡ mg/mL) ● Before 0.05 (0.05)§ ● After 1.1 (0.9)§ ● Doubling dose Δ 2.0 (1.5, 2.6)† NEA ● Before 0.3 (0.3)§ ● After 2.9 (2.5)§ ● Doubling dose Δ 1.7 (0.9, 2.4)†
Green[8]	2002	NR	NR	Budesonide 400 μg twice daily for 2 mo	VAS symptom scores were significantly improved in EA than NEA	● FEV_1 significantly increased in only EA ● Δ mean 0.21 (0.03, 0.39; P = .03)	● Doubling dose PC_{20} was significant increased in EA than NEA. ● Δ mean 1.1 (0.1, 2.2; P = .03)
Bacci[31]	2006	31 (21)	69 (46)	Beclomethasone diproprionate 500 μg twice daily for 4 wk	Symptom score and β_2-agonist used were improved in both EA and NEA	EA ● Before 87.9 ± 15.4 ● After 96.9 ± 14.5 ● Δ 9.0 ± 15.0 NEA ● Before 90.2 ± 17.3 ● After 91.2 ± 20.0 ● Δ 1.0 ± 18.8	EA (PC_{20}, μg) ● Before 135.0 ± 2.8 ● After 218.0 ± 5.2 ● Doubling dose Δ NR NEA ● Before 121.0 ± 3.7 ● After 185.0 ± 5.2 ● Doubling dose Δ NR
Pavord[34]	1999	NR	NR	Budesonide 400 μg twice daily for 2 mo	Improvement of VAS symptom scores was observed only in EA	EA ● Δ 0.1 (−5.0, 289.0) L† NEA ● Δ 0.1 (−193.0, 394.0) L†	EA (PC_{20},‡ mg/mL) ● Doubling dose Δ 2.1 (1.3, 3)† NEA ● Doubling dose Δ 0 (−1.2, 1.2)†

Data are presented as means ± SDs unless otherwise indicated. Doubling dose is difference in PC_{20} expressed by difference in doubling dose of adenosine monophosphate or methacholine.

ACQ, Asthma Control Questionnaire; *ACT,* asthma control test; *AQLQ,* Asthma Quality of Life Questionnaire; *NR,* not reported; *VAS,* visual analog score.

*Adenosine monophosphate challenge test.

†Mean or mean difference with 95% CI.

‡Methacholine challenge test.

§Median (interquartile range).

and paucigranulocytic asthma using specific definitions (see Table E7 in the Online Repository available at www.jaci-global.org). The predominant subtype of NEA was paucigranulocytic asthma in both patients receiving and not receiving ICS, with a prevalence ranging from 28% to 53%. Mixed granulocytic asthma was the least common subtype, with a prevalence of 2% to 8%.

Stability of asthma subtypes on reassessing sputum cytology

Among asthma patients not receiving ICS, McGrath et al[28] conducted sputum cytology 2 to 4 times over a 1-year study period and found that 47% had persistent NEA and 22% had persistent EA. Notably, 31% of patients exhibited sputum eosinophilia at least once during the study, a condition referred to as intermittent EA.

Three studies[29-31] reported the prevalence of EA and NEA before and after ICS receipt (see Table E8 in the Online Repository available at www.jaci-global.org). The NEA subtype became more prevalent across all 3 studies after ICS treatment. Disease of approximately 20% to 30% of patients initially classified as being NEA transitioned to the EA subtype over time. Given the limited effectiveness of ICS in treating NEA, it is plausible that this transition occurred independent of ICS therapy. This finding is particularly noteworthy compared to the prevalence of intermittent EA reported by McGrath et al.[28]

Clinical features and biomarkers associated with sputum eosinophilia

Table E9 in the Online Repository available at www.jaci-global.org summarizes studies evaluating the association between sputum eosinophilia, clinical features, and biomarkers. McGrath et al[28] reported that EA was associated with younger age, lower body mass index, and more frequent AHR. In contrast, NEA was linked to older age, nonatopic status, longer disease duration, and current smoking.[32,34]

Frossing et al[38] found that high blood eosinophil counts (BEC) and fractional exhaled nitric oxide (FENO) demonstrated a modest yet statistically significant agreement with sputum eosinophilia ($\kappa = 0.21$, $P = .0002$; $\kappa = 0.20$, $P = .0005$, respectively). Similarly, McGrath et al[28] reported that high BEC had a sensitivity of 72% and a specificity of 69%, while high FENO had a sensitivity of 64% and a specificity of 73%. Additionally, Cowan et al[30] identified an association between elevated FENO levels and sputum eosinophilia, favoring ICS response.

Risk of bias assessment of included studies focusing on ICS responses

Table E10 in the Online Repository available at www.jaci-global.org summarizes the risk of bias assessment of 9 studies using the Newcastle-Ottawa Scale. Eight studies with no serious concerns on population selection and exposure ascertainment were rated as high quality.[8,27-33] Only 1 study was rated as low quality due to population selection.[34]

Comparison of ICS responses between EA and NEA subtypes

Improvement of asthma symptoms. Six studies[8,28,30,31,33,34] compared ICS responses between EA and NEA subtypes using the improvement of asthma symptoms (Table II). Five studies demonstrated a significantly greater improvement in asthma symptoms and control favoring EA than NEA subtypes, while Bacci et al[31] and Godon et al[33] reported a significantly comparable decrease in asthma symptoms in both subtypes. Quantitative analysis could not be conducted because of the use of different measures to assess asthma symptoms across the studies.

Improvement of lung function. Six studies[8,28,30,31,33,34] assessed the improvement of FEV_1 after ICS treatment, but only 3 studies[30,31,33] reported sufficient data for quantitative analysis. The pooled estimate of FEV_1 improvement was significantly greater in EA than in NEA subtypes (SMD 0.79; 95% CI, 0.30, 1.27) as illustrated in Fig 4. The result of the leave-one-out sensitivity analysis did not differ from the main result (see Fig E3 in the Online Repository available at www.jaci-global.org).

Improvement of AHR. Five studies[8,30,31,33,34] assessed AHR after ICS treatment but only 2 studies[30,33] reported the PC_{20} changes from baseline at 4 weeks, and 2 studies[8,34] at 8 weeks for quantitative analysis. The pooled effects estimated at both time points for the improvement of AHR were significantly in favor of EA compared to the NEA subtypes. In a pooled analysis of 4 studies involving 212 patients, the overall changes from baseline in PC_{20} were significantly greater in EA than in NEA subtypes (SMD 1.34; 95% CI, 0.29, 2.40), as shown in Fig 5. The subgroup analysis by the duration of ICS treatment demonstrated a consistent treatment effect. A leave-one-out sensitivity analysis result revealed a similar effect to the main result (see Fig E4 in the Online Repository available at www.jaci-global.org).

GRADE assessment for primary and secondary outcomes

Table III summarizes the GRADE assessment for the NEA prevalence and treatment responses to ICS. For the NEA prevalence, the certainty of evidence was rated as very low in patients who were ICS naive and those with mixed ICS naive and ICS withdrawal, while that was rated as low in those receiving ICS. For FEV_1 outcomes, the certainty of evidence was rated as low, while for PC_{20} outcomes, it was rated as very low.

DISCUSSION

This systematic review involved 18 studies with a total of 3,533 patients. Our meta-analysis revealed a prevalence of NEA subtype in adolescents and adults with mild-to-moderate asthma who were ICS naive at 40% and in those who were receiving ICS at 69%. Reevaluation of sputum cytology revealed that approximately 20% to 30% of disease initially diagnosed as NEA transitioned to the EA subtype. EA demonstrated a favorable response to ICS, whereas NEA exhibited limited effectiveness.

The subtype prevalence of adults and adolescents with mild-to-moderate asthma displays considerable heterogeneity across studies, influenced by several factors. First, variation arose from the different thresholds used to define sputum eosinophilia. However, most studies included in this review used the

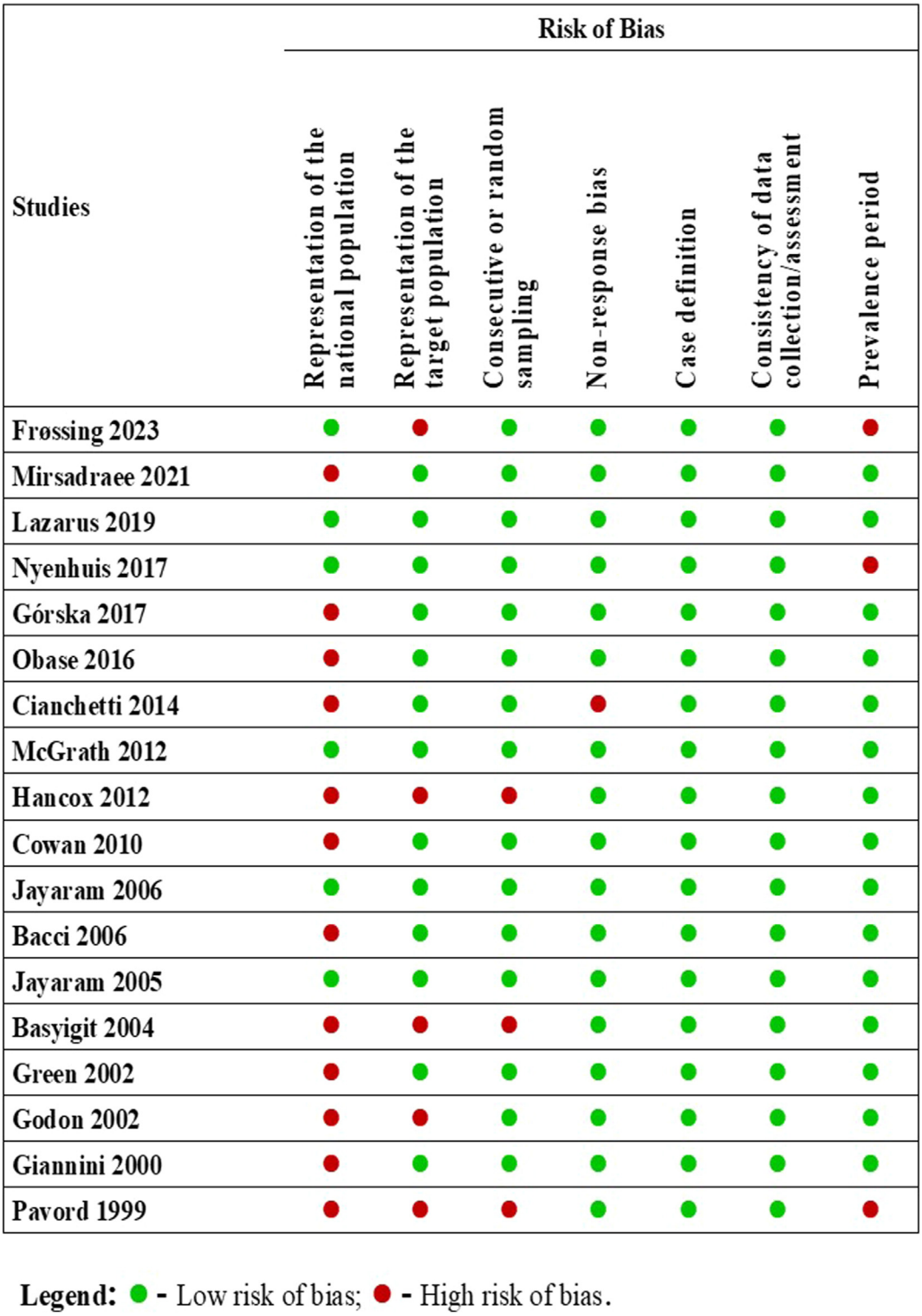
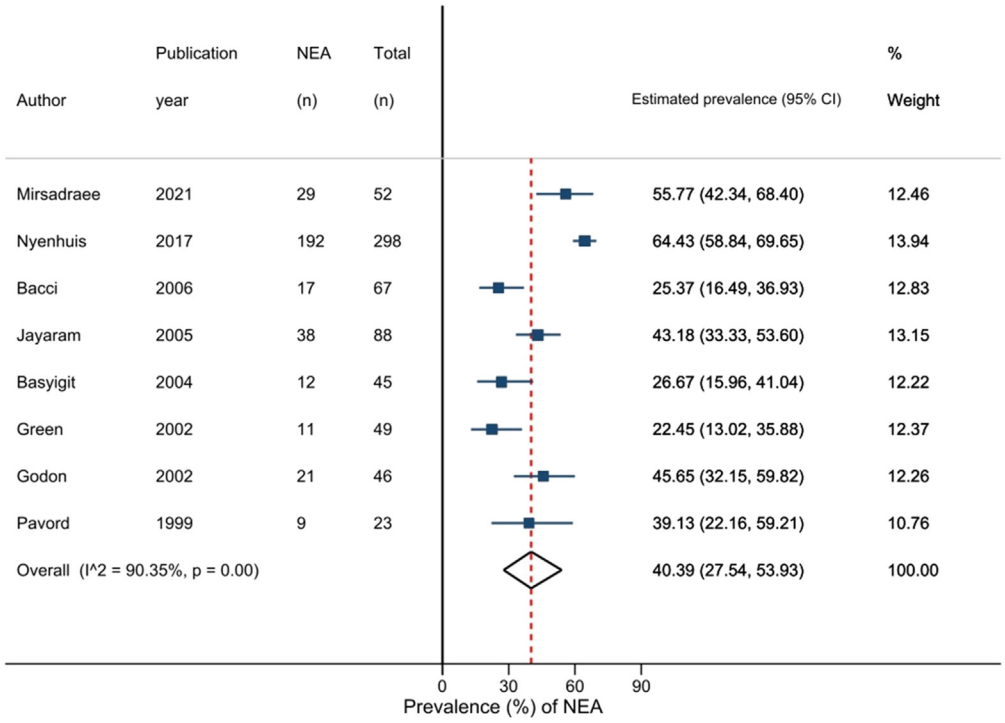


FIG 2. Risk of bias assessment of included studies. *Green* indicates low risk of bias of each domain; *red,* high risk.

recommended standardizing threshold of 2% to 3% sputum eosinophils, which should reasonably represent the optimal cutoff.[39] Second, asthma medications, particularly ICS and systemic corticosteroids, potentially modify airway inflammatory cell profiles by reducing eosinophils and increasing neutrophils.[40] Consequently, subtype prevalence in patients who are ICS naive and have no history of systemic corticosteroids treatment should reflect a more valid subtype than in those receiving such

A **NEA prevalence in patients with ICS-naïve**



B **NEA prevalence in patients with mixed ICS-naïve and ICS withdrawal**

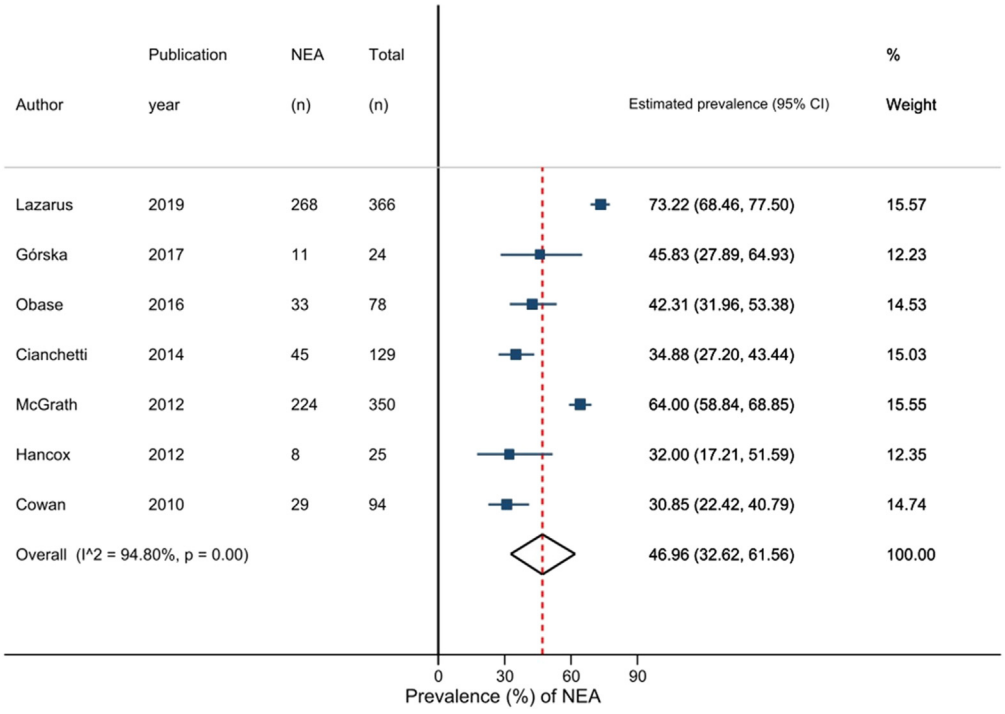


FIG 3. Forest plots showing pooled noneosinophilic subtype prevalence of adolescents and adults with mild-to-moderate asthma who were **(A)** ICS naive and who were **(B)** ICS naive with ICS withdrawal.

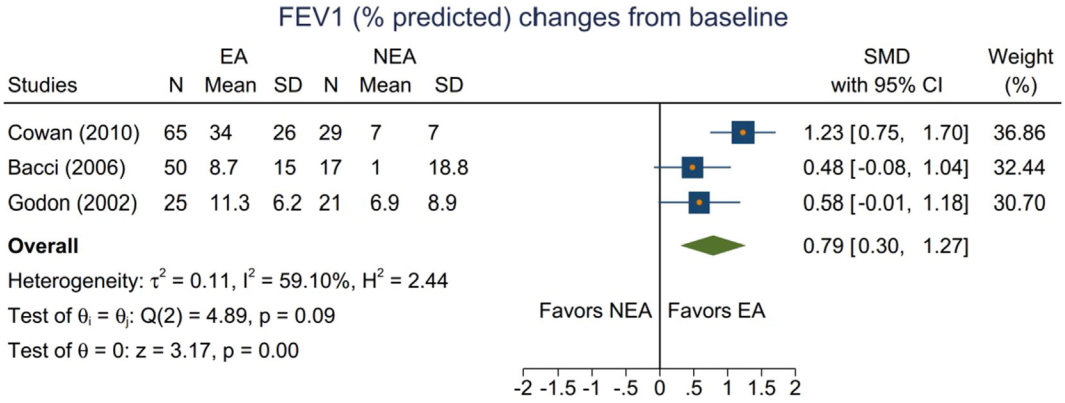


FIG 4. Forest plot showing pooled SMD of mean changes from baseline in FEV_1 after treatment with ICS compared between EA and NEA.

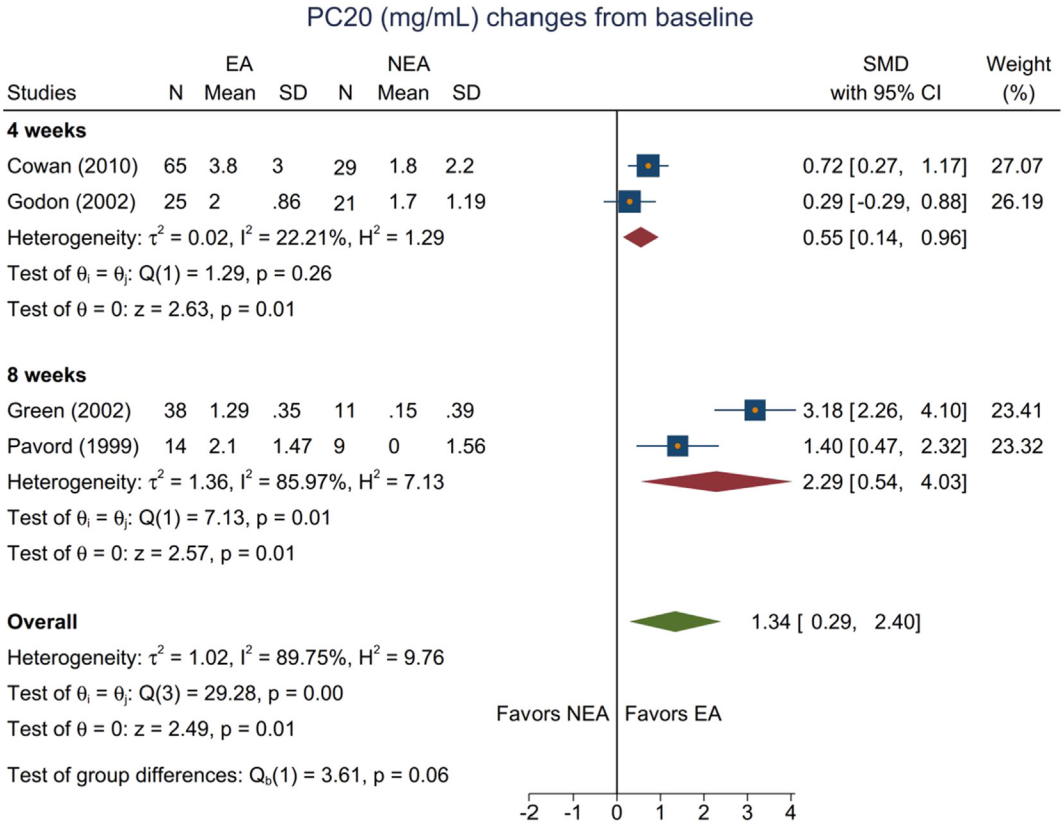


FIG 5. Forest plot showing pooled SMD of mean changes from baseline in provocative concentration causing 20% decrease in FEV_1 (PC_{20}) after ICS treatment compared between EA and NEA.

medication. Third, inflammatory cell types are generally susceptible to various factors, including age, body mass index, and smoking status. This systematic review demonstrated that EA was associated with younger age, lower body mass index, and increased AHR. In contrast, NEA was linked to older age, nonatopic status, overweight, smoking, and longer disease duration. These factors may account for the transition from NEA to EA observed in some individuals in our study. In contrast, as indicated by previous evidence,[41] certain patients initially identified as NEA may retain this classification on subsequent evaluation. Fourth, before diagnosing NEA, it is crucial to exclude airway infections, bronchiectasis, chronic obstructive pulmonary diseases, and other conditions that mimic asthma.[41,42]

Despite being a promising biomarker, sputum cytology is usually impractical in clinical settings. In pursuit of alternative biomarkers, Covar et al[43] examined BEC, FENO, and total IgE levels in untreated mild asthma and found the area under the curve within the range of 0.7 to 0.8, indicating their moderate correlation with sputum eosinophilia. The sensitivity and specificity of BEC and FENO to predict sputum eosinophilia were also reported

TABLE III. GRADE quality rating of pooled outcomes

	Certainty assessment							No. of patients		Effect			
Analysis	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EA	NEA	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
NEA subtype prevalence of mild-to-moderate asthma with ICS naive	8	Multi design*	Not serious	Serious†	Not serious	Serious‡	None§	668¶	329	—	EP 40.39 (27.54, 53.93)	⨁◯◯◯ Very low	Critical
NEA subtype prevalence of mild-to-moderate asthma with mixed ICS-naive and ICS withdrawal	7	Multi design*	Not serious	Serious†	Not serious	Serious‡	None§	1,066¶	618	—	EP 46.96 (32.62, 61.56)	⨁◯◯◯ Very low	Critical
NEA subtype prevalence of mild-to-moderate asthma receiving ICS	8	Multi design*	Not serious	Serious†	Not serious	Not serious‡	None§	2,109¶	1,639	—	EP 69.68 (60.34, 78.30)	⨁⨁◯◯ Low	Critical
FEV_1 (% predicted) changes from baseline (follow-up at 4 weeks)	3	Observational studies	Not serious	Not serious	Not serious	Not serious‡	None§	140	67	—	SMD 0.79 (0.30, 1.27)	⨁⨁◯◯ Low	Critical
PC_{20} doubling dose (mg/mL) changes from baseline (follow-up at 4+ weeks)	4	Observational studies	Not serious‖	Serious†	Not serious	Not serious‡	None§	142	70	—	SMD 1.34 (0.29, 2.40)	⨁◯◯◯ Very low	Important

EP, Estimated prevalence.
*Prevalence was not directly affected by study design. Therefore, certainty of pooled outcomes was not rated down.
†There was a statistically high level of heterogeneity across studies.
‡Pooled result was considered precise if CI width (2 sides) did not exceed 20% in prevalence outcome or crossed more than 3 thresholds for secondary outcomes (FEV_1 [% predicted] and PC_{20}).
§Publication bias was not assessed because there were too few studies to permit analysis.
¶Total patients.
‖One of 4 studies was rated as low quality. Sensitivity analysis by removing high-risk studies confirmed primary result to be robust.

at only 60% to 70%.[28] Some individuals with asthma might exhibit increased FENO and/or total IgE levels without sputum eosinophilia, while others may have sputum eosinophilia without concurrent blood eosinophilia, implying potential independence among these biomarkers.[38] The correlation of those 3 biomarkers (BEC, FENO, and total IgE) was generally weaker in mild-to-moderate asthma than in severe asthma.[38] These observations align with the findings of Couillard et al,[44] which demonstrated that blood and sputum biomarkers delineate distinct compartments of airway inflammation.

Concerning biomarkers in predicting ICS responses, Pavord et al[45] have recently conducted a *post hoc* analysis using data from the NOVEL START[46] study in adults with mild asthma. They found that high baseline BEC was positively associated with the effectiveness of ICS, whereas, at low BEC, ICS tended to perform worse than short-acting β_2-agonists.[45] In contrast, ICS-formoterol was effective regardless of baseline BEC.[45] Another *post hoc* analysis using data from the SIENA study[22] found that none of BEC, FENO, or sputum eosinophilia had an excellent correlation with ICS responses.[47] Given the challenge of identifying a single biomarker specific to sputum eosinophilia, combining easily measured biomarkers such as BEC, FENO, and total IgE with a thorough assessment of clinical features is essential for accurate asthma subtype classification.

To our knowledge, this is the first comprehensive systematic review and meta-analysis on subtype prevalence and ICS response that is based on sputum cytology in adolescents and adults with mild-to-moderate asthma. We have identified that NEA affects a considerable proportion of asthma patients. A shift to the EA subtype was observed in approximately 20% to 30% of cases initially classified as NEA after repeating sputum cytology. Given the limited effectiveness of ICS therapy in managing NEA, it is essential to explore alternative treatment options. However, there were some limitations. First, the number of included studies was small. However, we performed a comprehensive search, encompassing 4 databases, and did not impose exclusion criteria based on date or language of publication. Second, the included studies differed in their methodologies, potentially contributing to the statistical heterogeneity observed in this review. Third, the prevalence of NEA may have been overestimated because of a single sputum cytology assessment in most studies, which likely led to an underdiagnosis of patients with transient sputum eosinophilia. Additionally, the inclusion of patients who currently smoke and those with a history of long-term smoking in some studies may also have contributed to the high reported prevalence of NEA and inadvertently included individuals with asthma–chronic obstructive pulmonary disease overlap in the study populations. Fourth, some outcome values used during ICS responsiveness analysis were not directly reported in the included original articles, so they had to be extracted from graphs, imputed, or calculated from reported surrogated values. This potentially affected the quality of data and the pooled results. However, we believe that the impact is minimal because standard methods were used as references. In addition, leave-one-out sensitivity analyses for all outcomes showed minimal differences compared to the main results.

In conclusion, on the basis of sputum cytology analysis, our systematic review revealed varying prevalence rates of EA and NEA among adolescents and adults with mild-to-moderate asthma. A transition from NEA to EA could occur in some patients over time. EA responded favorably to ICS, whereas NEA lacked similar benefits. The impracticality of sputum cytology in clinical settings underscores the importance of integrating clinical phenotypes and alternative biomarkers during the initial assessment to steer proper management strategies.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: C. Wongsa has received honoraria for scientific lectures from A. Menarini, AstraZeneca, GSK, Novartis, Sanofi, Takeda, and Abbott; and research support from Abbott and Sanofi. J. A. Bernstein has received funding from Novartis, Genentech, Amgen, Sanofi Regeneron, GSK, and Astra Zeneca. T. Thongngarm has received honoraria for scientific lectures from A. Menarini, Astra-Zeneca, GSK, Novartis, P&G, Sanofi, Takeda, and Viatris; has received research support from Abbott, Sanofi, and Viatris; and has served on the advisory board for Sanofi and Viatris. The rest of the authors declare that they have no relevant conflicts of interest.

Declaration of generative AI– and AI-assisted technologies: The graphical abstract was created by Canva Pro/Chamard Wongsa. After the creation process, the authors carefully reviewed and edited all content, and they take full responsibility for the accuracy and integrity of this publication.

Key messages

- **NEA exists in a significant proportion of adolescents and adults with mild-to-moderate asthma.**
- **Some patients may experience a shift from NEA to EA over time, necessitating a comprehensive diagnostic assessment in clinical practice resulting from the varying response to ICS across asthma subtypes.**

REFERENCES

1. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention, 2024 update. Available at: https://ginasthma.org/archived-reports/.
2. de Farias CF, Amorim MM, Dracoulakis M, Caetano LB, Santoro IL, Fernandes AL. Nasal lavage, blood or sputum: which is best for phenotyping asthma? Respirology 2017;22:671-7.
3. Carr TF, Zeki AA, Kraft M. Eosinophilic and noneosinophilic asthma. Am J Respir Crit Care Med 2018;197:22-37.
4. Schleich FN, Manise M, Sele J, Henket M, Seidel L, Louis R. Distribution of sputum cellular phenotype in a large asthma cohort: predicting factors for eosinophilic vs neutrophilic inflammation. BMC Pulm Med 2013;13:11.
5. Shi B, Li W, Hao Y, Dong H, Cao W, Guo J, et al. Characteristics of inflammatory phenotypes among patients with asthma: relationships of blood count parameters with sputum cellular phenotypes. Allergy Asthma Clin Immunol 2021;17:47.
6. Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: assessment and identification using induced sputum. Respirology 2006;11:54-61.
7. Demarche S, Schleich F, Henket M, Paulus V, Van Hees T, Louis R. Detailed analysis of sputum and systemic inflammation in asthma phenotypes: are paucigranulocytic asthmatics really non-inflammatory? BMC Pulm Med 2016;16:46.
8. Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. Thorax 2002;57:875-9.
9. Lemiere C, Tremblay C, FitzGerald M, Aaron SD, Leigh R, Boulet LP, et al. Effects of a short course of inhaled corticosteroids in noneosinophilic asthmatic subjects. Can Respir J 2011;18:278-82.
10. Contoli M, Pauletti A, Rossi MR, Spanevello A, Casolari P, Marcellini A, et al. Long-term effects of inhaled corticosteroids on sputum bacterial and viral loads in COPD. Eur Respir J 2017;50:1700451.
11. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editors. Cochrane handbook for systematic reviews of interventions. 2nd ed. Chichester (United Kingdom): Wiley; 2019.

12. 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.
13. van de Schoot R, de Bruin J, Schram R, Zahedi P, de Boer J, Weijdema F, et al. An open source machine learning framework for efficient and transparent systematic reviews. Nat Mach Intell 2021;3:125-33.
14. Quan Y, Tytko T, Hui B. Utilizing ASReview in screening primary studies for meta-research in SLA: a step-by-step tutorial. Research Methods in Applied Linguistics 2024;3:100101.
15. van Haastrecht M, Sarhan I, Yigit Ozkan B, Brinkhuis M, Spruit M. SYMBALS: a systematic review methodology blending active learning and snowballing. Front Res Metr Anal 2021;6:685591.
16. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol 2012;65:934-9.
17. Cardoso-Fernandes A, Blumenthal KG, Chiriac AM, Tarrio I, Afonso-Joao D, Delgado L, et al. Frequency of severe reactions following penicillin drug provocation tests: a Bayesian meta-analysis. Clin Transl Allergy 2021;11:e12008.
18. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed May 18, 2024.
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
20. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175-91.
21. Granholm A, Alhazzani W, Moller MH. Use of the GRADE approach in systematic reviews and guidelines. Br J Anaesth 2019;123:554-9.
22. Lazarus SC, Krishnan JA, King TS, Lang JE, Blake KV, Covar R, et al. Mometasone or tiotropium in mild asthma with a low sputum eosinophil level. N Engl J Med 2019;380:2009-19.
23. Mirsadraee M, Azmoon B, Ghaffari S, Abdolsamadi A, Khazdair MR. Effect of Propolis on moderate persistent asthma: a phase two randomized, double blind, controlled clinical trial. Avicenna J Phytomed 2021;11:22-31.
24. Jayaram L, Pizzichini E, Lemiere C, Man SF, Cartier A, Hargreave FE, et al. Steroid naive eosinophilic asthma: anti-inflammatory effects of fluticasone and montelukast. Thorax 2005;60:100-5.
25. Giannini D, Di Franco A, Cianchetti S, Bacci E, Dente FL, Vagaggini B, et al. Analysis of induced sputum before and after withdrawal of treatment with inhaled corticosteroids in asthmatic patients. Clin Exp Allergy 2000;30:1777-84.
26. Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemiere C, Pizzichini E, et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. Eur Respir J 2006;27:483-94.
27. Nyenhuis SM, Krishnan JA, Berry A, Calhoun WJ, Chinchilli VM, Engle L, et al. Race is associated with differences in airway inflammation in patients with asthma. J Allergy Clin Immunol 2017;140:257-65.e11.
28. McGrath KW, Icitovic N, Boushey HA, Lazarus SC, Sutherland ER, Chinchilli VM, et al. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. Am J Respir Crit Care Med 2012;185:612-9.
29. Hancox RJ, Cowan DC, Aldridge RE, Cowan JO, Palmay R, Williamson A, et al. Asthma phenotypes: consistency of classification using induced sputum. Respirology 2012;17:461-6.
30. Cowan DC, Cowan JO, Palmay R, Williamson A, Taylor DR. Effects of steroid therapy on inflammatory cell subtypes in asthma. Thorax 2010;65:384-90.
31. Bacci E, Cianchetti S, Bartoli M, Dente FL, Di Franco A, Vagaggini B, et al. Low sputum eosinophils predict the lack of response to beclomethasone in symptomatic asthmatic patients. Chest 2006;129:565-72.
32. Basyigit I, Yildiz F, Ozkara SK, Boyaci H, Ilgazli A. Inhaled corticosteroid effects both eosinophilic and non-eosinophilic inflammation in asthmatic patients. Mediators Inflamm 2004;13:285-91.
33. Godon P, Boulet LP, Malo JL, Cartier A, Lemiere C. Assessment and evaluation of symptomatic steroid-naive asthmatics without sputum eosinophilia and their response to inhaled corticosteroids. Eur Respir J 2002;20:1364-9.
34. Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. Lancet 1999;353:2213-4.
35. Gorska K, Paplinska-Goryca M, Nejman-Gryz P, Goryca K, Krenke R. Eosinophilic and neutrophilic airway inflammation in the phenotyping of mild-to-moderate asthma and chronic obstructive pulmonary disease. COPD 2017;14:181-9.
36. Obase Y, Shimoda T, Kishikawa R, Kohno S, Iwanaga T. Trigger of bronchial hyperresponsiveness development may not always need eosinophilic airway inflammation in very early stage of asthma. Allergy Rhinol (Providence) 2016;7:1-7.
37. Cianchetti S, Bacci E, Ruocco L, Pavia T, Bartoli ML, Cardini C, et al. Are sputum eosinophil cationic protein and eosinophils differently associated with clinical and functional findings of asthma? Clin Exp Allergy 2014;44:673-80.
38. Frossing L, Klein DK, Hvidtfeldt M, Obling N, Telg G, Erjefalt JS, et al. Distribution of type 2 biomarkers and association with severity, clinical characteristics and comorbidities in the BREATHE real-life asthma population. ERJ Open Res 2023;9.
39. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.
40. Nguyen LT, Lim S, Oates T, Chung KF. Increase in airway neutrophils after oral but not inhaled corticosteroid therapy in mild asthma. Respir Med 2005;99:200-7.
41. Haldar P, Pavord ID. Noneosinophilic asthma: a distinct clinical and pathologic phenotype. J Allergy Clin Immunol 2007;119:1043-52.
42. Nair P, Surette MG, Virchow JC. Neutrophilic asthma: misconception or misnomer? Lancet Respir Med 2021;9:441-3.
43. Covar R, Lazarus SC, Krishnan JA, Blake KV, Sorkness CA, Dyer AM, et al. Association of sputum eosinophilia with easily measured type-2 inflammatory biomarkers in untreated mild persistent asthma. J Allergy Clin Immunol Pract 2024;12:960-9.e6.
44. Couillard S, Shrimanker R, Chaudhuri R, Mansur AH, McGarvey LP, Heaney LG, et al. Fractional exhaled nitric oxide nonsuppression identifies corticosteroid-resistant type 2 signaling in severe asthma. Am J Respir Crit Care Med 2021;204:731-4.
45. Pavord ID, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. Lancet Respir Med 2020;8:671-80.
46. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Controlled trial of budesonide–formoterol as needed for mild asthma. N Engl J Med 2019;380:2020-30.
47. Krishnan JA, Lazarus SC, Blake KV, Sorkness CA, Covar R, Dyer AM, et al. Biomarkers to predict response to inhaled corticosteroids and long-acting muscarinic antagonists in adolescents and adults with mild persistent asthma. Ann Am Thorac Soc 2022;19:372-80.