Received: 11 January 2024 | Accepted: 17 January 2024

DOI: 10.1111/pai.14078

SYSTEMATIC REVIEW

WILEY

A systematic review and meta-analysis on absolute eosinophil counts and the risk of asthma in preschool children with wheezing: An EAACI Task Force Report

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Funding information
European Academy of Allergy and Clinical Immunology (EAACI)

Editor: Ömer Kalayci

Abstract

Preschool children with wheezing disorders pose diagnostic and therapeutic challenges and consume substantial healthcare resources. Peripheral eosinophil blood count (EBC) has been proposed as a potential indicator for future asthma development. This review by the European Academy of Allergy and Clinical Immunology (EAACI) Preschool Wheeze Task Force aimed to provide systematic evidence for the association between increased EBC and the risk of future asthma, as well as to identify potential cutoff values. In February 2023, a search of PubMed, EMBASE, and Cochrane Library databases was conducted to identify studies comparing EBCs in preschool children with wheezing who continued to wheeze later in life and those who did not. Included observational studies focused on children aged <6 years with a wheezing disorder, assessment of their EBCs, and subsequent asthma status. No language or publication date restrictions were applied. Among the initial 3394 studies screened, 10 were included in the final analysis, involving 1225 patients. The data from these studies demonstrated that high EBC in preschool children with wheezing is associated

with future asthma development, with odds ratios of 1.90 (95% CI: 0.45–7.98, $p = .38$), 2.87 (95% CI: 1.38–5.95, $p < .05$), and 3.38 (95% CI: 1.72–6.64, $p < .05$) for cutoff values in the <300, 300–449, and ≥450 cells/μL ranges, respectively. Defining a specific cutoff point for an elevated EBC lacks consistency, but children with EBC >300 cells/μL are at increased risk of asthma. However, further research is needed due to the limitations of the included studies. Future investigations are necessary to fully elucidate the discussed association.

KEYWORDS
asthma, eosinophil, eosinophil blood count, preschool, wheezing

1 | INTRODUCTION

Preschool children with wheezing disorders present a diagnostic and therapeutic challenge and consume significant healthcare resources.[1] Wheezing in preschoolers encompasses various clinical and pathological phenotypes.[2,3] Around 30 to 50 percent of preschool-aged children experience wheezing episodes, often triggered by viral respiratory tract infections.[4,5] While most cases of wheezing are mild and transient, some infants develop recurrent and severe episodes requiring medical review, hospitalization, and specialized diagnosis and management.[6]

Recurrent wheezing can be an early indication of asthma, a condition characterized by airway remodeling, hyperresponsiveness, immune system activation, and excessive mucus production.[6] These processes can lead to educational and social impairments, significantly affecting the quality of life if appropriate and timely treatment is not received.[7,8] Consequently, there is a pressing need to identify markers that can accurately predict the risk of developing asthma later in life, particularly for patients in their early childhood.[9]

One potential option is eosinophil blood counts (EBCs), a cost-effective and easily accessible test. Eosinophils play a role in the development of allergic asthma and contribute to allergic inflammation.[10] Currently, EBCs (≥4%) have been used in clinical practice to identify wheezing children at a higher risk of asthma, mainly as a minor criterion in established predictive indices.[11,12] However, the routine use of EBCs lacks systematic evidence, as existing recommendations and cutoff values primarily rely on expert opinion.[2,13]

The European Academy of Allergy and Clinical Immunology (EAACI) has formed the Preschool Wheeze Task Force in order to prepare recommendations on the diagnostics of wheezy breathing in children. In order to provide sufficient data support for those upcoming recommendations, we undertook this systematic review and meta-analyses, following a previously registered protocol.

This systematic review aims to consolidate available data on the association between elevated EBCs in preschool wheezing and the likelihood of future atopic asthma.

Key message

Preschool-aged children with wheezing who present with eosinophil blood counts of over 300 cells per microliter are at an increased risk of future asthma.

2 | METHODS

This review was performed by the members of the EAACI Preschool Wheeze Task Force and select external specialists invited by the members of the Task Force, comprising methodologists, pediatricians, allergists, pediatric pneumonologists, immunologists, public health specialists, biostatisticians, and other clinicians, practising in five countries: Denmark, Finland, Poland, Sweden, and the USA.

In November 2020, three databases (PubMed, Embase, and the Cochrane Library) were screened using the following search strategy (formatted for PubMed):

> (preschool child OR infant* OR infancy OR toddler OR pre-school OR kindergarten OR nursery OR preschool*) AND (eosinophil* OR eosinocyte* OR eosinophil blood count* OR EBC OR eosinophil count test* OR eosinophil count* OR peripheral blood eosinophil*) AND (asthma* OR wheez* OR bronchiolitis OR bronchitis OR LTRI OR lower respiratory tract infection* lower respiratory tract illness*).

The review was registered in the PROSPERO database at the University of York (ID: CRD42020221322).

After removing duplicate entries, the titles and abstracts of retrieved articles were independently screened by four researchers (AA, MC, KM, and JT) using the following eligibility criteria:

- Sample: Children with wheezing disorders aged <6 years.
- Phenomenon of interest: Wheezing at preschool age and asthma in later life.
- Design: All types of observational studies.

- Evaluation: EBC (absolute or relative).
- Research type: Qualitative, quantitative, and mixed methods research. There were no restrictions on the language of the articles. Papers focusing on treatment response were excluded as the focus was on diagnostics.

The results of the title and abstract screening were cross-checked between the four researchers. Thirty records were selected for full-text review, but two full texts were unavailable. Seven researchers (AA, KB, BC, MC, SJ, KM, and JT) independently assessed the remaining 28 articles, and the results were cross-checked. At the end of the 2020 review process, eight articles met the inclusion criteria and were included in the meta-analysis. From each study, the researchers (AA, KB, BC, MC, SJ, KM, and JT) tallied the number of patients with EBC over and under a threshold, specified by each study individually, who would or would not develop asthma in later life, in order to present the data as odds ratios (OR). Sensitivity analysis was performed by removing studies with the lowest and highest OR in a given group.

In February 2023, an additional search was conducted to identify articles published during the review process. Using the same search strategy and databases, 477 documents were retrieved (after removing duplicates). After a review by two independent researchers (AA and MC), three studies from the update were eligible for inclusion in the analysis but lacked crucial data. We contacted the authors of the included articles and requested unpublished data.[14–16] Two out of the three research teams agreed to collaborate and shared their data, which was included in the final meta-analyses. Thus, these two studies were added to the originally identified eight studies, resulting in a total of 10 studies.

2.1 | Software

EndNote X9 and EndNote 20 were used for the initial review process. Data compilation was done using Microsoft Excel. Review Manager 5.4 was used for conducting the meta-analysis and calculating the associated statistics.[17]

2.2 | Risk-of-bias assessment

We assessed the risk of bias using the "Quality In Prognosis Studies" (QUIPS) tool.[18] Four researchers independently evaluated bias across six subdomains: participation bias, attrition bias, prognostic factors measurement, outcome measurement, study confounding, and statistical analysis and presentation.

2.3 | Statistical analysis

The meta-analysis was conducted using the Mantel–Haenszel method for random effects, based on data extracted from the included studies. The chi-squared test was used to test for subgroup differences, and the I^2 statistic was used to estimate data heterogeneity. I^2 values between 0% and 40% were considered to represent low heterogeneity, 40%–60% moderate heterogeneity, and I^2 over 60% was considered high heterogeneity. Prediction intervals were calculated when appropriate.

3 | RESULTS

After removing duplicate records, a total of 3394 entries were screened through title and abstract review. Thirty-six articles underwent full-text review, and ultimately, 10 articles met the inclusion criteria and were included in the final analysis. Additional details about the review stages and reasons for exclusion can be found in the study flowchart (Figure 1).

To address the variation in cutoff points used among the studies, we grouped them based on commonly used ranges in EBC research. For instance, a study using a cut-off value of 84 cells/μL would be analyzed in the <300 cells/μL group, while a study using a cutoff value of 300 cells/μL would be assigned to the 300–449 cells/μL group. One study[14] provided data for multiple groups, which were analyzed separately to avoid inflating sample sizes.

3.1 | <300 cells/μL

Two studies utilized cutoff points in this range (Figure 2). One study[19] employed a cut-off point of ≥84 cells/μL, corresponding to ≥1% of white blood cells in the analysis. The other study used a cut-off of 100 cells/μL.[14] The combined sample size in this group was 235 patients. The OR in this group was not statistically significant at 1.90 (95% CI: 0.45–7.98) with significant heterogeneity ($I^2 = 74\%$). Due to the result being statistically not significant, prediction intervals were not calculated. The studies had a moderate[19] and low[14] risk-of-bias scores, with the domains of attrition, prognostic factor measurement, and study confounding most contributing to the overall increase of their risk of bias (Figure 3).

3.2 | 300–449 cells/μL

Five studies employed a cutoff point between 300 and 449 cells/μL,[14,20–23] involving a total of 974 subjects (Figure 2). The overall OR in this group was 2.87 (95% CI: 1.38–5.95) with substantial heterogeneity ($I^2 = 68\%$) (Figure 2). The standard deviation of the prediction interval (SDPI) was calculated as 0.714, with a prediction interval ranging from 0.396 to 20.814. The probability that the OR was less than 1 in future studies was estimated to be 10.7%. The risk of bias varied in this group, with three studies having a low risk-of-bias score,[14,20,21] one study having a moderate risk,[23] and one study having a high risk,[22] mainly due to study confounding bias (Figure 3).

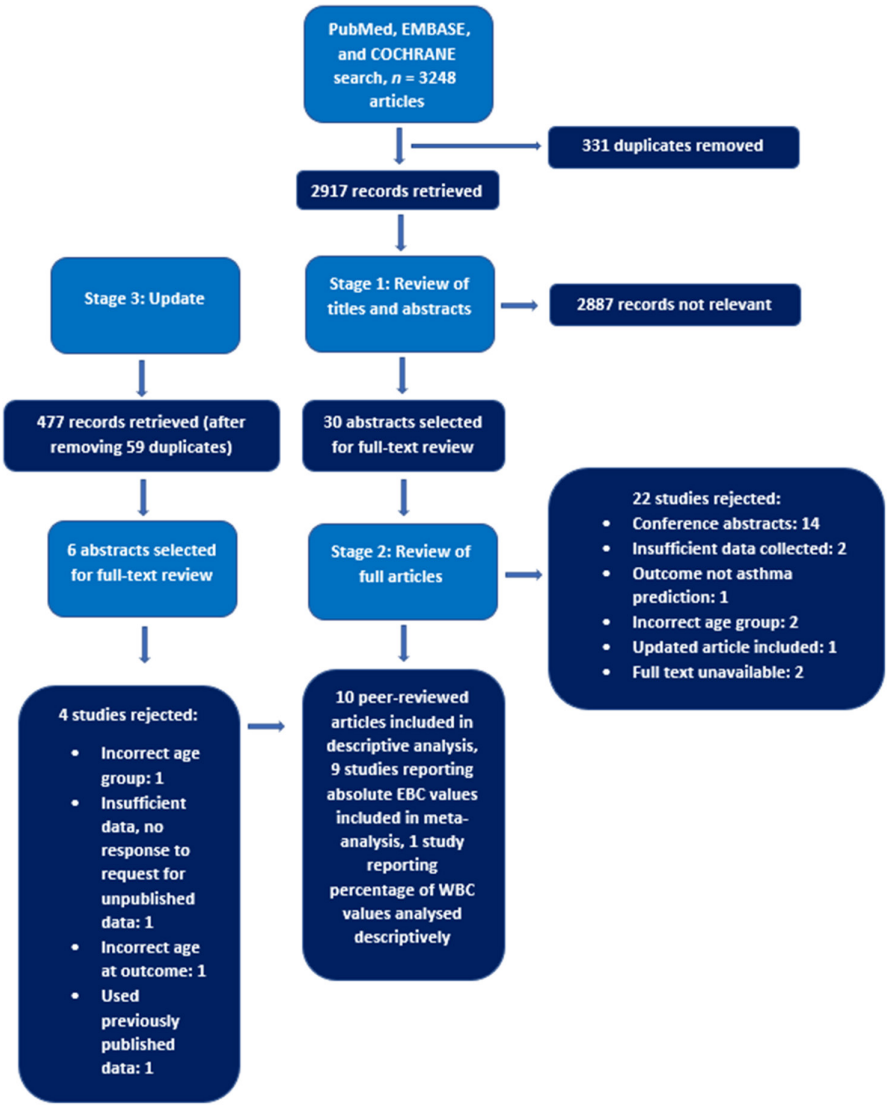

FIGURE 1 Summary of the number of studies included and excluded from the analysis.

3.3 | ≥450 cells/μL

Four studies fell within the ≥450 cells/μL range,[14,24–26] involving a total of 500 children (Figure 2). The OR was 3.38 (95% CI: 1.72–6.64), with moderate heterogeneity ($I^2 = 51\%$) (Figure 2). The SDPI was calculated as 0.534, and the prediction interval ranged from 0.618 to 18.485. The prediction interval was calculated as 2.688 to 8.044. The probability of achieving a reverse result in future studies was estimated to be 5.3%. The risk of bias in this group ranged from low to moderate (Figure 3).

3.4 | Percentage of WBC

Two studies reported cutoff values of eosinophilia as percentage of white blood cells, one at 1% with an OR of 4.50 (1.18, 17.21)[19] and the second at 2.5% with an OR of 2.137 (1.507, 3.03).[27] The discrepancy between the cut-offs was deemed to be too large and, as such, these studies were excluded from further analysis. The risk of bias was moderate for one study[19] and high for the other,[27] primarily due to increased participation and attrition bias.

3.5 | Risk-of-bias assessment

Detailed results of the risk of bias assessment can be found in Figure 3. In summary, two studies had a high overall risk of bias,[22,27] five had a moderate risk of bias,[19,23–26] and three had a low risk of bias.[14,20,21] Attrition bias contributed the most to the overall risk of bias across the retrieved studies, with only a single study achieving a low risk of bias score in that domain.[20]

The overall risk of bias was compiled from scores from the six subdomains (Figure 3).

3.6 | Sensitivity analysis

Sensitivity analysis was conducted in the 300–449 cells/μL and ≥450 cells/μL groups by excluding studies with the highest and

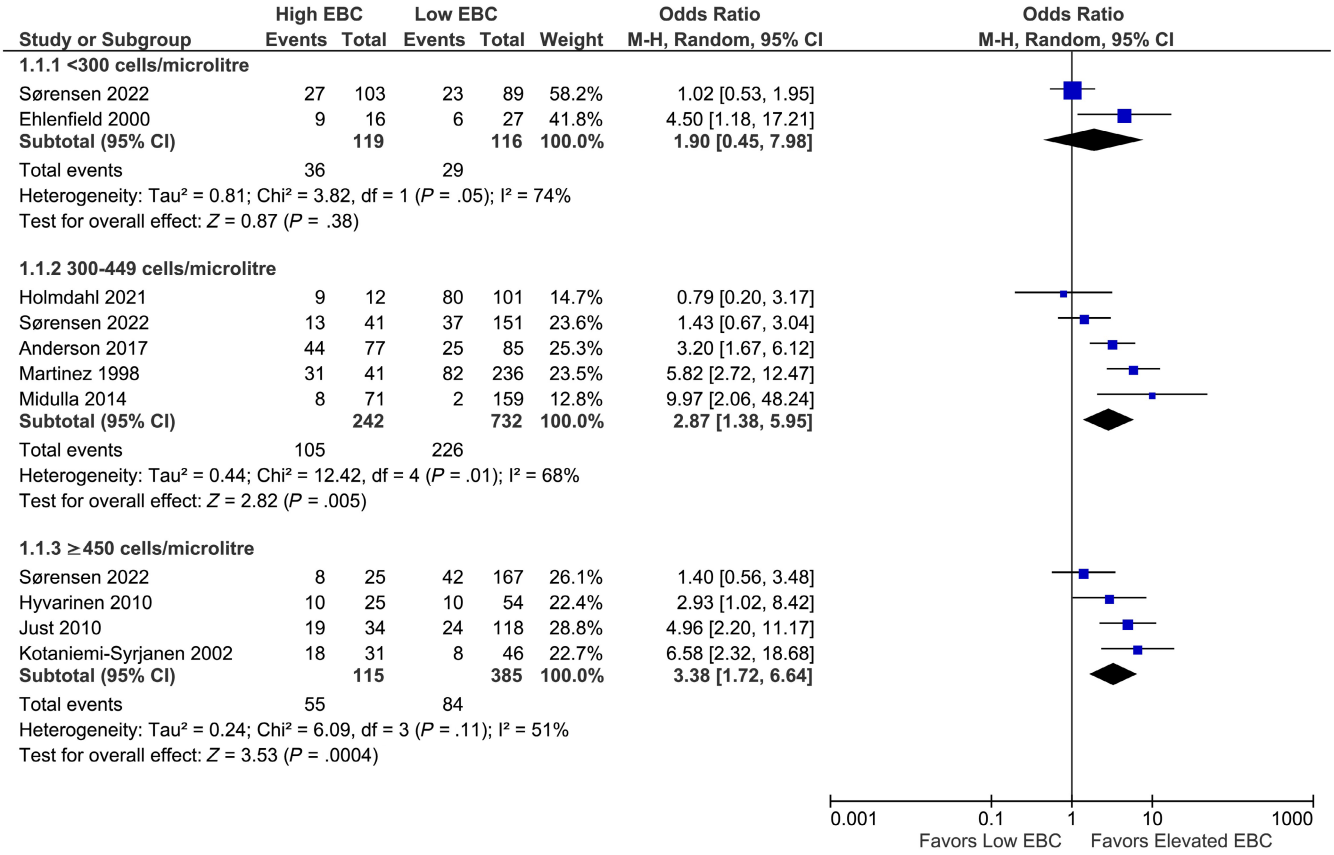

FIGURE 2 Forest plot depicting the associations between elevated eosinophil blood count and risk of asthma, divided into subgroups based on the cut-off point used (>300 cells/μL, 300–449 cells/μL, and ≥450 cells/μL). The right side of the vertical line favors low eosinophil counts in the prediction of asthma. CI, confidence interval; I^2: heterogeneity statistic; OR, odds ratio.

lowest OR in their respective groups. The exclusion of these studies did not significantly impact the statistical significance of the overall results in these groups. Detailed results in the form of forest plots can be found in the supplementary material (Figure S1 in the Online Repository).

4 | DISCUSSION

This systematic review shows a clear link between elevated EBC in children with a history of wheezing at preschool age and subsequent asthma diagnosis. The EBC is the most easily accessible and cheapest marker and predictor of possible allergic sensitization. According to our findings, there is potential for utilizing this tool as an evidence-based approach to identify wheezy children who may have an increased risk of asthma at an early age. As demonstrated by our meta-analysis, the odds of asthma increase with an increase in EBC. Despite the lack of a reliably established cutoff, our research shows that preschool children with wheezing whose EBCs are higher than 300 cells/μL are at an increased risk of future asthma and might, as suggested by other research, benefit from regular clinical assessments and early introduction of treatment.[28,29] In recent years, research considering the utility of peripheral blood eosinophils in predicting lung function improvement or tailoring asthma treatment has shown promising results.[30,31] However, there exists conflicting reports about the utility of early introduction of asthma treatment in preventing longitudinal complications, that is, airway remodeling and development of other obstructive disorders in children.[32] Nevertheless, patients at an increased risk of asthma still require regular medical attention to ensure adequate symptom control, even in the absence of evidence for disease trajectory-altering treatment. There appears to be a lack of consistency within the available literature on defining what constitutes an elevation in EBC, as revealed by this analysis. The identified studies used seven different cutoff values to define the same condition—an EBC elevation. Such inconsistencies can be found in research regarding EBCs in various disorders, as discussed by Jesenak et al. in their work on molecular insights and clinical functions of eosinophils and the clinical effects of targeted eosinophil depletion.[33]

This lack of uniformity likely stems from the researchers' varied approaches employed during study design and the lack of a concrete, firmly established cutoff point for an elevated EBC in the studied age group. According to current clinical practice and the results of our study, the most popular current cutoff seems to be 300 cells/μL.[34–36] Further work is required, however, since the justification for its everyday use is insufficient, as it is not only derived from expert opinion and not systematic or experimental work but also commonly justified by guidelines on the management of chronic obstructive

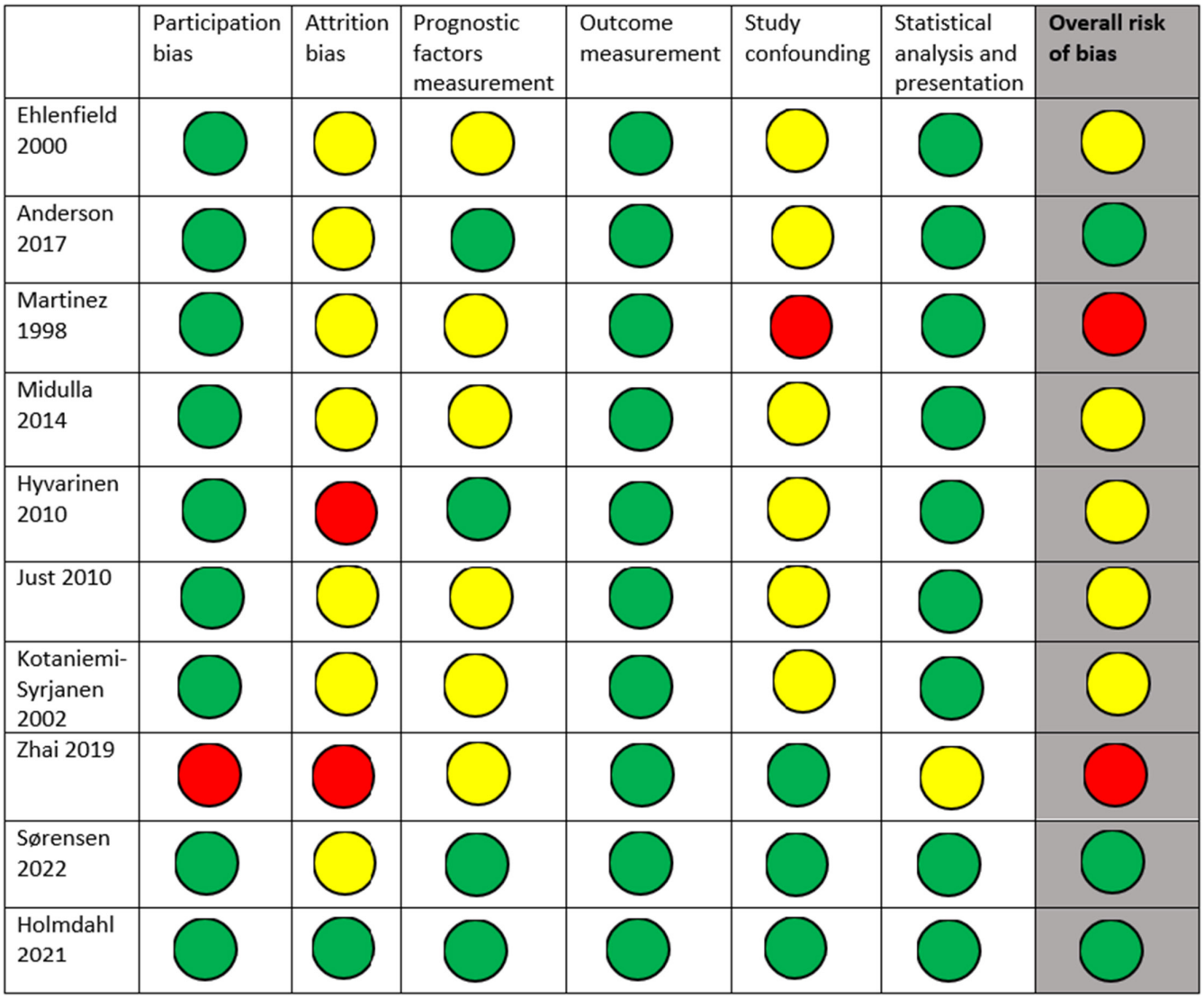

FIGURE 3 Risk-of-bias summary, divided into domains and overall. Green—low risk of bias; yellow—moderate risk of bias; red—high risk of bias.

pulmonary disorder in adults.[2,11,37] Furthermore, as suggested by the OR for future asthma increasing with the increase of EBC, the indicator might exhibit a dose–response association with the risk of future asthma. As such, it might not have a true cutoff value, instead having a directly proportional relationship with the risk of asthma. This conclusion, however, is impossible to make based solely on the data available in the published literature and should be investigated in a study designed specifically for that purpose.

This study has several strong points. To our knowledge, it is the first attempt to systematically review available data on the association of particular EBC levels during preschool wheezing and the odds of future asthma. As such, it provides a robust foundation for future research and recommendations. Furthermore, it reveals a need for more consistency between researchers when choosing a cutoff point, the lack of which might contribute to clinical inconsistencies and needs to be addressed by future guidelines or recommendations for clinical practice.

Our study has several potential limitations. First, the conclusions of this study may be weakened by the relatively high risk-of-bias scores of reviewed articles. Second, as with all review articles, our study is prone to publication bias. Third, the small number of relevant articles provides lower statistical power and weakens conclusions, particularly in the <300 cells/μL group. Fourth, while the included studies all dealt with preschool aged children, due to the nature of systematic reviews, specific ages of recruitment and ages at follow-up differed between the studies. As eosinophil levels have been shown to change with age, this introduces a certain level of bias to the final analysis.[38] Fifth, the results from the source studies are not adjusted for the presence of atopic dermatitis, which, apart from being a common comorbidity of asthma, also is associated with elevated peripheral EBC.[39,40] Finally, although the OR is highest in the ≥450 cells/μL group, it does not allow us to define this number as an optimal cutoff clearly. Such a conclusion could be made in an individual patient data analysis or a well-designed observational study.

In summary, this meta-analysis reinforces the association between elevated EBC and the risk of future asthma. Eosinophil blood count are a cost-effective and easily accessible tool for assessing future asthma risk in preschool children with wheezing and, as such, can aid physicians in making informed therapeutic decisions.

This study provides important data for the upcoming EAACI recommendations on the diagnosis of preschool wheezing and sheds some light on the areas of the subject, which require further investigation. A large, focused, prospective, multi-center cohort study is required to set a reliable cutoff point or predictive model for EBCs as predictors of asthma in the preschool population.

USE OF ARTIFICIAL INTELLIGENCE DISCLOSURE STATEMENT

During the preparation of this work, the authors used OpenAI's ChatGPT 3.5 in order to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

AUTHOR CONTRIBUTIONS

Aleksander Adamiec: Conceptualization; methodology; software; data curation; formal analysis; visualization; writing – review and editing; writing – original draft; investigation; validation. **Maja Cieślik:** Investigation; formal analysis; writing – original draft; writing – review and editing. **Katarzyna Mączka:** Investigation; formal analysis; writing – original draft; writing – review and editing. **Joanna Tarnoruda:** Investigation; formal analysis; writing – original draft; writing – review and editing. **Signe Jensen:** Investigation; formal analysis; writing – review and editing. **Bo Chawes:** Investigation; formal analysis; writing – review and editing. **Klaus Bønnelykke:** Investigation; formal analysis; writing – review and editing. **Jon R. Konradsen:** Investigation; formal analysis; writing – review and editing. **Cilla Söderhäll:** Investigation; formal analysis; writing – review and editing. **Heidi Makrinioti:** Investigation; formal analysis; writing – review and editing; methodology. **Carlos A. Camargo Jr:** Methodology; formal analysis; writing – review and editing; investigation. **Kohei Hasegawa:** Investigation; formal analysis; methodology; writing – review and editing. **Dominika Ambrożej:** Investigation; formal analysis; writing – review and editing. **Tuomas Jartti:** Project administration; resources; writing – review and editing; funding acquisition. **Marek Ruszczyński:** Methodology; investigation; validation; formal analysis; supervision; writing – review and editing. **Wojciech Feleszko:** Conceptualization; methodology; supervision; funding acquisition; project administration; resources; writing – original draft; writing – review and editing; visualization; validation.

FUNDING INFORMATION

This systematic review was supported by the European Academy of Allergy and Clinical Immunology (EAACI) under the EAACI Task Force on Preschool Wheeze, Working Group Infections (2022/23), budget reference number: 40316.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/pai.14078.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Adamiec A, Cieślik M, Mączka K, et al. A systematic review and meta-analysis on absolute eosinophil counts and the risk of asthma in preschool children with wheezing: An EAACI Task Force Report. *Pediatr Allergy Immunol*. 2024;35:e14078. doi:10.1111/pai.14078