International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

INPLASY202630063

doi: 10.37766/inplasy2026.3.0063

Received: 18 March 2026

Published: 18 March 2026

**Corresponding author:**
YU-TZU LI

tsz9903028@gmail.com

**Author Affiliation:**
Changhua Christian Hospital.

# Eosinophil-derived neurotoxin as a biomarker for diagnosis, disease severity, and prediction in children with atopic dermatitis and allergic rhinitis: a protocol for a systematic review and meta-analysis

Wu, CT; Yang, YT; Li, YT; Wu, TH; Ying, TH; Lue, KH.

## ADMINISTRATIVE INFORMATION

**Support -** This study received no specific funding.

**Review Stage at time of this submission -** Preliminary searches.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202630063

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 March 2026 and was last updated on 18 March 2026.

## INTRODUCTION

**Review question / Objective** The aim of this systematic review and meta-analysis is to evaluate the role of eosinophil-derived neurotoxin (EDN), also known as eosinophil protein X (EPX), as a biomarker for: (1) diagnosis of atopic dermatitis (AD) and allergic rhinitis (AR) in children; (2) assessment of AD disease severity; and (3) prediction of allergic disease development, including the atopic march. The review will address the following questions: (a) Are EDN/EPX levels significantly elevated in children with AD or AR compared to healthy controls? (b) Does EDN/EPX correlate with AD disease severity? (c) Can early-life EDN/EPX levels predict subsequent development of allergic diseases? (d) What is the diagnostic accuracy of serum EDN for allergic disease screening in children?

**Rationale** Atopic dermatitis and allergic rhinitis are among the most prevalent chronic inflammatory conditions in children. Current biomarkers such as total IgE and blood eosinophil counts have notable limitations in specificity and in reflecting eosinophil activation status. EDN/EPX is an eosinophil granule protein with superior analytical reproducibility compared to eosinophil cationic protein (ECP) and can be measured non-invasively in urine. Despite accumulating evidence suggesting EDN/EPX as a promising biomarker, no systematic review or meta-analysis has comprehensively evaluated its diagnostic, severity-monitoring, and predictive utility specifically for pediatric AD and AR. Previous reviews have focused primarily on asthma or were narrative without quantitative synthesis. This systematic review aims to fill this evidence gap.

**Condition being studied** Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by pruritic eczematous lesions, affecting approximately 15–20% of children worldwide. Allergic rhinitis (AR) is a symptomatic disorder of the nose induced by IgE-mediated inflammation of the nasal mucosa, affecting 10–40% of the pediatric population. Both conditions share common immunopathological features

including Th2-mediated immune responses and eosinophilic tissue infiltration. The atopic march describes the progressive sequence in which AD in infancy precedes development of food allergy, asthma, and AR later in childhood.

## METHODS

**Search strategy** A comprehensive literature search will be conducted in five electronic databases: PubMed, Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov, from inception through March 2026. The search strategy uses three concept groups combined with AND: (1) Biomarker: ("eosinophil-derived neurotoxin" OR "EDN" OR "eosinophil protein X" OR "EPX" OR "RNase 2"); (2) Disease: ("atopic dermatitis" OR "atopic eczema" OR "eczema" OR "allergic rhinitis" OR "atopic march"); (3) Population: ("child" OR "pediatric" OR "paediatric" OR "infant" OR "adolescent"). Wildcard truncation will be used where supported. No language or date restrictions will be applied. Reference lists of included studies and relevant reviews will be manually screened.

**Participant or population** Children and adolescents aged 0–18 years with physician-diagnosed atopic dermatitis, allergic rhinitis, or both, using validated diagnostic criteria. Healthy controls without allergic diseases will serve as comparison groups. Studies exclusively enrolling adults (>18 years) without separate pediatric subgroup analysis will be excluded.

**Intervention** Not applicable. This is a diagnostic/biomarker review, not an intervention review. The index test is EDN or EPX measurement in any biological specimen (serum, plasma, urine, sputum, or nasal lavage fluid).

**Comparator** For diagnostic comparisons: healthy controls without atopic diseases. For severity correlations: validated clinical severity scores (e.g., SCORAD, Rajka-Langeland grading). For predictive analyses: children who did not develop allergic diseases during follow-up.

**Study designs to be included** Cross-sectional studies, prospective and retrospective cohort studies, case-control studies, and randomized controlled trials reporting EDN/EPX levels in children with AD or AR. Case reports, case series with fewer than 10 participants, review articles, editorials, conference abstracts without original data, and letters will be excluded.

**Eligibility criteria** Inclusion: (1) Enrolled children aged 0–18 years; (2) Measured EDN or EPX in any biological specimen; (3) Included participants with AD, AR, or both; (4) Reported quantitative data on EDN/EPX levels; (5) Original research in peer-reviewed journals.
Exclusion: (1) Exclusively adult populations without pediatric subgroup; (2) Reviews, editorials, conference abstracts, case reports; (3) EDN/EPX only in non-allergic conditions without AD/AR comparator; (4) Duplicate publications; (5) Full text unavailable.

**Information sources** PubMed, Embase, Cochrane Library, Web of Science, and ClinicalTrials.gov. Additional sources: manual screening of reference lists of included studies and relevant review articles.

**Main outcome(s)** (1) Standardized mean difference (SMD) of EDN/EPX levels between children with AD and healthy controls. (2) Correlation coefficient between EDN/EPX levels and AD disease severity scores. (3) Standardized mean difference of EDN levels between children with AR and healthy controls.

**Additional outcome(s)** (1) Predictive associations of early-life EDN/EPX with subsequent allergic disease development (odds ratios, hazard ratios). (2) Diagnostic accuracy of serum EDN (AUC, sensitivity, specificity, cutoff values). (3) Treatment monitoring response of EDN/EPX levels.

**Data management** All records will be imported into Rayyan software for systematic review management (Ouzzani et al., 2016). Two reviewers will independently screen titles/abstracts and full texts. Data will be extracted using a pre-designed standardized form. Discrepancies will be resolved by discussion and consensus. When studies report medians and IQR, conversion to means and SDs will follow the method described by Wan et al. (2014). Correlation coefficients will be transformed to Fisher's z values for pooling (Fisher, 1921).All records will be imported into Rayyan software for systematic review management (Ouzzani et al., 2016). Two reviewers will independently screen titles/abstracts and full texts. Data will be extracted using a pre-designed standardized form. Discrepancies will be resolved by discussion and consensus. When studies report medians and IQR, conversion to means and SDs will follow the method described by Wan et al. (2014). Correlation coefficients will be transformed to Fisher's z values for pooling (Fisher, 1921).All records will be imported into Rayyan software for systematic review management. Two reviewers will independently screen titles/abstracts and full texts. Data will be extracted using a pre-designed

standardized form. Discrepancies will be resolved by discussion and consensus. When studies report medians and IQR, conversion to means and SDs will follow the Wan et al. method. Correlation coefficients will be transformed to Fisher's z values for pooling.

**Quality assessment / Risk of bias analysis** Observational and diagnostic studies will be assessed using QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2), evaluating four domains: patient selection, index test, reference standard, and flow and timing. Randomized controlled trials will be assessed using the Cochrane Risk of Bias 2 (RoB2) tool. Quality assessment will be performed independently by two reviewers. Results will be visualized using the robvis R package.

**Strategy of data synthesis** Meta-analysis will be performed when at least two studies report comparable outcomes. For continuous outcomes (EDN/EPX levels), standardized mean differences (Hedges' g) will be calculated using random-effects models (DerSimonian-Laird method). For correlation data, Fisher's z-transformed coefficients will be pooled using fixed-effect inverse variance models and back-transformed for interpretation. Statistical heterogeneity will be assessed using Cochran's Q test ($p < 0.10$) and the $I^2$ statistic. Outcomes not amenable to pooling will undergo structured narrative synthesis. All analyses will be performed using RevMan 5.4, with $p < 0.05$ considered significant.

**Subgroup analysis** Pre-specified subgroup analyses include: (1) specimen type (serum EDN vs. urinary EPX); (2) disease type (AD vs. AR); (3) severity correlation target (clinical severity score vs. itch VAS vs. eosinophil count); (4) age group (infants <2 years vs. older children). Subgroup differences will be tested using interaction tests.

**Sensitivity analysis** Sensitivity analyses will include: (1) excluding studies with high risk of bias; (2) excluding studies requiring median-to-mean conversion; (3) using alternative effect size estimators where applicable. Due to the small number of studies (<10), funnel plots and formal publication bias tests will not be conducted.

**Language restriction** No language restrictions will be applied.

**Country(ies) involved** Taiwan (primary institution).

**References** Wan et al.: Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
Ouzzani et al.: Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016;5:210.
Fisher: Fisher RA. On the probable error of a coefficient of correlation deduced from a small sample. Metron. 1921;1:3–32.
Chia-Ta Wu and Ya-Ting Yang contributed equally to this work and should be considered co-first authors. Ko-Huang Lue and Tsung-Ho Ying are co-corresponding authors.

**Keywords** eosinophil-derived neurotoxin; eosinophil protein X; atopic dermatitis; allergic rhinitis; biomarker; children; systematic review; meta-analysis.

**Dissemination plans** The results of this systematic review will be submitted for publication in a peer-reviewed journal in the field of allergy, immunology, or pediatrics. Findings may also be presented at relevant national or international conferences.

**Contributions of each author**
Author 1 - CHIA-TA WU - Conceiving and designing the review; developing the search strategy; screening and selecting studies; data extraction; risk of bias assessment; performing statistical analysis; drafting and writing the manuscript.
Email: allenpig1102@gmail.com
Author 2 - Ya-Ting Yang - Designing the review; screening and selecting studies; data extraction; risk of bias assessment; data conversion and verification; drafting and revising the manuscript.
Email: melody199404@yahoo.com.tw
Author 3 - Yu-Tzu Li - Screening and selecting studies; data extraction; quality assessment; creating tables and figures; reviewing and editing the manuscript.Contribution: Screening and selecting studies; data extraction; quality assessment; creating tables and figures; reviewing and editing the manuscript.
Email: tsz9903028@gmail.com
Author 4 - Ting-Hsuan Wu - Literature search and database management; data extraction; risk of bias assessment; reviewing and editing the manuscript.
Email: ab118tw@gmail.com
Author 5 - Tsung-Ho Ying - Supervising the review process; providing methodological guidance; interpreting the results; critically revising the manuscript for important intellectual content; final approval of the manuscript.

Email: ying.steve@gmail.com
Author 6 - Ko-Huang Lue - Conceiving the review; providing clinical expertise and oversight; interpreting the results; critically revising the manuscript for important intellectual content; final approval of the manuscript.
Email: cshy095@csh.org.tw