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Neutrophil percentage-to-albumin ratio (NPAR) as a biomarker for asthma: a cross-sectional analysis of NHANES data

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Abstract

Objective This study aimed to access the neutrophil percentage-to-albumin ratio (NPAR) as a potential biomarker for asthma risk and to explore its association with asthma incidence in a nationally representative adult population.

Methods We analyzed cross-sectional data from 17,800 adults in the National Health and Nutrition Examination Survey (NHANES 2009–2018). NPAR was calculated as the ratio of neutrophil percentage to serum albumin concentration. Multivariable logistic regression models adjusted for demographic, socioeconomic, clinical, and laboratory covariates were employed to assess NPAR-asthma associations. Missing data were addressed via multiple imputations, and model performance was evaluated using receiver operating characteristic (ROC) curves with bootstrap validation. Restricted cubic splines analyzed non-linear relationships, while subgroup analyses tested effect heterogeneity across demographic and clinical strata. Sensitivity analyses compared complete-case and imputed datasets.

Results Elevated NPAR levels were strongly associated with increased asthma risk. In fully adjusted models, each one-unit increase in NPAR corresponded to a 2.6% rise in asthma prevalence (adjusted OR = 1.026, 95% CI: 1.008–1.045, $P = 0.0046$). ROC curve analysis demonstrated an AUC of 0.699 for NPAR in predicting asthma. Subgroup analyses revealed effect modification by sex, race, and cardiovascular disease history, though interaction terms did not meet Bonferroni-adjusted significance thresholds. Restricted cubic spline analyses indicated a U-shaped dose-response relationship, with minimal risk observed at NPAR values of 12–15, suggesting dual pathological mechanisms: oxidative stress susceptibility at lower NPAR values and neutrophilic inflammation dominance at higher values.

Conclusion This study provides the first epidemiological evidence supporting NPAR as an independent biomarker for asthma risk. The U-shaped association highlights the complex interplay between systemic inflammation and oxidative stress in asthma pathogenesis. While NPAR offers a cost-effective and accessible tool for risk stratification, its moderate predictive performance underscores the need for complementary biomarkers to enhance clinical utility. Future research should integrate serial NPAR measurements and multi-omics profiling to validate its role in asthma management.

Keywords Asthma, Neutrophil percentage-to-albumin ratio, Biomarker, Chronic inflammation, NHANES study

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Introduction

Asthma is a chronic, heterogeneous respiratory disease characterized by symptoms such as shortness of breath, cough, wheezing, and chest tightness [1]. The underlying causes of asthma include airway inflammation, which leads to its symptoms [2]. Asthma is the most common chronic respiratory diseaseldwide and occurs twice as often as chronic obstructive pulmonary disease (COPD). The World Health Organization (WHO) estimates that approximately 339 million people globally have asthma, resulting in approximately 250,000–350,000 deaths annually [3]. Over time, uncontrolled asthma can cause various complications, such as chronic obstructive pulmonary disease and cor pulmonale. These complications can worsen patient outcomes, threaten overall health, and create significant economic and social challenges [4].

Inflammation is vital to the development of asthma [5, 6]. Asthma develops through the involvement of several immune cell types, such as eosinophils, T lymphocytes, macrophages, and neutrophils. During an asthma attack, T lymphocytes residing in the airway mucosa activate and produce a wide range of cytokines. Eosinophils are the primary cells in the inflammatory infiltrate, but other types, including mast cells, basophils, neutrophils, monocytes, and macrophages, are also present [7]. The ratios of common blood markers are clinically significant as diagnostic biomarkers. For example, the neutrophil-to-lymphocyte ratio (NLR) is recognized as an important indicator of systemic inflammation, particularly in pulmonology. Huang et al. [7] found that the NLR is valid, easy to use, and a crucial marker for asthma. However, emerging evidence suggests that the neutrophil percentage-to-albumin ratio (NPAR), a novel inflammatory biomarker, may offer superior predictive value compared to traditional markers such as NLR and C-reactive protein (CRP) [8].

Unlike NLR, which solely reflects granulocyte-lymphocyte balance, NPAR integrates two critical biological pathways: neutrophil-driven inflammation and albumin-modulated systemic antioxidant capacity [9, 10]. This dual-component design addresses the limitations of single-parameter biomarkers. For instance:

1. Diagnostic Accuracy: In a meta-analysis of chronic obstructive pulmonary disease (COPD) cohorts, NPAR achieved an AUC of 0.82 for predicting exacerbations, significantly outperforming NLR (AUC = 0.68) and CRP (AUC = 0.61) [11].
2. Prognostic Value: NPAR independently predicted 1-year mortality in critically ill patients with acute kidney injury (HR = 1.44, 95% CI: 1.21–1.71), whereas NLR and CRP showed weaker associations [12].
3. Cost-Effectiveness: NPAR is derived from routine complete blood count (CBC) and albumin measurements, avoiding specialized assays for CRP or cytokine profiling [13, 14].

The NPAR has recently emerged as a significant blood marker [15, 16]. NPAR is a robust biomarker that integrates neutrophil percentage and albumin level components. It offers an affordable and readily available measure of systemic inflammation. Early studies have shown that the NPAR can predict the prognosis of acute kidney injury, cardiogenic shock, myocardial infarction, and cancer [12]. No studies have examined the association between NPAR and asthma incidence. This study aims to clarify how the NPAR is related to asthma occurrence, thus providing insights into the correlation between inflammatory markers and respiratory outcomes.

Methods

Data sources

For this cross-sectional study, we analyzed data from the National Health and Nutrition Examination Survey (NHANES), available at http://www.cdc.gov/nchs/nhanes. The NHANES program is managed by the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC). The participants in the NHANES first complete a household interview, after which they are invited to undergo a comprehensive evaluation at a mobile examination center (MEC). During this evaluation, participants receive a physical examination, take specific anthropometric measurements, and undergo various laboratory tests. As a result, the NHANES database offers reliable and extensive population data, making it an essential resource for population-level assessments [17].

Study population

The data on participants were from five cycles of the NHANES published from 2009 to 2018, with 49,693 participants representing an estimated 196 million people in the United States. The inclusion criteria included people aged ≥ 20 years who were not pregnant. According to NHANES, asthma is assessed via the Medical Conditions Questionnaire (MCQ). Asthma is defined by a positive response to the following question: "Have you ever been told you have asthma?" This method of identifying asthma has been used in various previous NHANES studies [18].

This study examined comprehensive data on asthma and the NPAR from 49,693 participants. After several exclusion criteria, including individuals under 20 years of age (n = 20,858), pregnant participants (n = 315), those uncertain about their pregnancy status (n = 432), and cases with missing data (n = 8,562), as well as those excluded due to missing NPAR information (n = 1,710), were applied, the final analysis was conducted on 17,816

eligible participants. Among these, 17,800 individuals had a diagnosis of asthma, with 2,475 responding "yes" to specific inquiries and 15,325 responding "no." (Fig. 1).

Neutrophil-percentage-to-albumin ratio (NPAR)

The NPAR was calculated as the neutrophil percentage (%) ratio to serum albumin concentration (g/dL), following standardized protocols from recent NHANES studies [13, 19]. This composite biomarker integrates two key pathophysiological dimensions: (1) neutrophil percentage, which quantifies acute-phase inflammatory response as validated in chronic respiratory disease cohorts [15], and (2) serum albumin, a recognized marker of nutritional status and antioxidant capacity whose decline correlates with systemic inflammation severity [12]. The methodological validity of this ratio has been extensively demonstrated in large-scale epidemiological research, including its predictive utility for mortality in chronic obstructive pulmonary disease (AUC = 0.74, NHANES 2011–2018) [13] and chronic kidney disease progression (OR = 1.32 per unit increase, NHANES 2009–2018) [19]. Compared with single-parameter biomarkers, NPAR's dual-component design offers improved sensitivity for detecting chronic inflammatory states, as evidenced by multi-cohort analyses [7, 16].

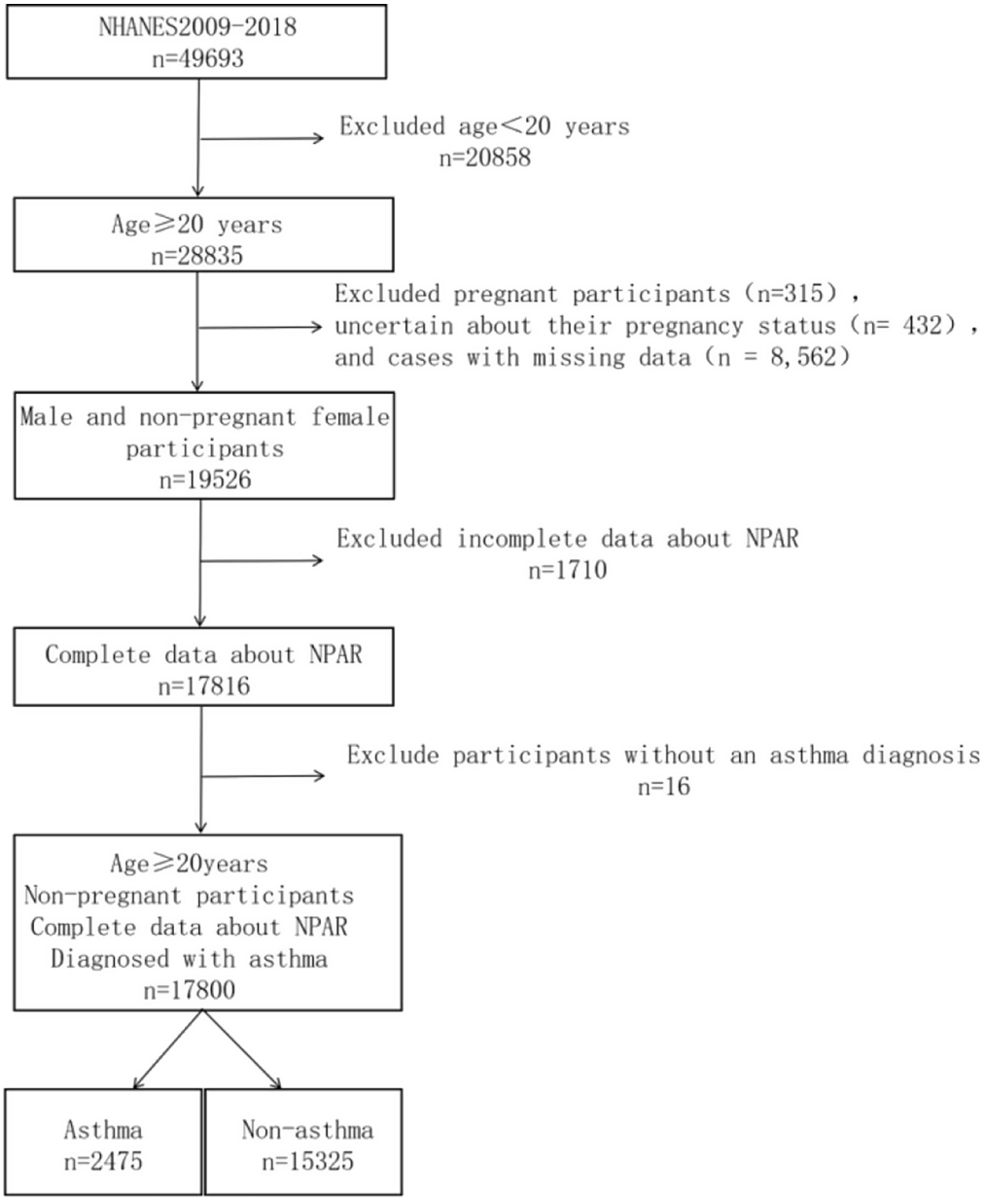

Fig. 1 Flowchart of participant selection. NHANES, National Health and Nutrition Examination Survey; NPAR, neutrophil percentage-to-albumin ratio

Covariates

To identify potential confounders in the relationship between the NPAR and asthma within multivariable-adjusted models, we considered a range of factors including age, sex, race, education level, poverty-income ratio (PIR), alcohol consumption, smoking habits, body mass index (BMI), the presence of cardiovascular disease (CVD), high blood pressure (HBP), and diabetes, as well as laboratory measures such as the albumin level, neutrophil percentage, vitamin D level, eosinophil number, lymphocyte number, red cell distribution width, and platelet count. In addition, we also calculated the dietary inflammatory index(DII) of the participants [20].

Demographic characteristics

There are five racial categories: Mexican American, other Hispanics, non-Hispanic Whites, non-Hispanic Blacks, and other races. Educational attainment encompasses three distinct levels: individuals who have not completed high school, those who possess a high school diploma, and individuals who have pursued education beyond high school. The PIR was classified into three categories: low (< 1.5), medium (1.5–3.5), and high (> 3.5). Alcohol consumption status was assessed via the question "ALQ130 - Average number of alcoholic drinks per day during the past 12 months." Smoking status is categorized into three groups: never-smokers (individuals who have smoked fewer than 100 cigarettes in their lifetime), former smokers (individuals who have smoked at least 100 cigarettes but do not currently smoke), and current smokers (individuals who have smoked at least 100 cigarettes and currently smoke either occasionally or daily).

Comorbidities

Subjects with a history of congestive heart failure, coronary heart disease, angina, or heart attack are classified as having cardiovascular disease. High blood pressure (HBP) was defined as meeting at least one of the following criteria: (1) an average systolic blood pressure (SBP) ≥ 140 mmHg, (2) an average diastolic blood pressure (DBP) ≥ 90 mmHg, or (3) current use of prescribed antihypertensive medication. This definition follows the clinical criteria used in NHANES protocols and reflects both measured values and medication history. Diabetes was identified through a questionnaire or other criteria, including fasting blood glucose levels of ≥ 7 mmol/L or current use of diabetes medications or insulin. The situation of close relatives having asthma is obtained by answering the survey question "Close relative had asthma?" An answer of 1 indicates yes, whereas an answer of 2 indicates no.

Missing value handling

To address missing data while preserving the validity of our analyses, we implemented a rigorous multiple imputation workflow using IBM SPSS Statistics (Version 29.0). This process adhered to established methodological guidelines and included four sequential phases: (1) pre-imputation diagnostics, (2) imputation model specification, (3) post-imputation validation, and (4) sensitivity analyses (Table 1).

Phase 1: pre-imputation diagnostics

Prior to imputation, we systematically evaluated missing data patterns through a series of preliminary analyses. The Missing Values Analysis module used monotone and arbitrary missingness schematics to visualize missing data patterns across variables. Little's Missing Completely at Random (MCAR) test was conducted to assess the plausibility of the MCAR assumption, complemented by auxiliary variable analysis to identify potential predictors of missingness. Variables with excessive missingness (> 40%) were excluded from imputation models following current recommendations.

Phase 2: imputation model specification

The multiple imputation procedure utilized the Fully Conditional Specification (FCS) method with predictive mean matching for continuous variables and logistic regression for categorical variables. Twenty imputed datasets were generated, exceeding Rubin's rule requiring at least five imputations given our maximum fraction of missing information (0.18). Continuous variables were constrained within biologically plausible ranges (e.g., body mass index 15–50 kg/m^2) to prevent implausible imputed values. Auxiliary variables showing moderate correlations ($r = 0.3$–0.7) with incomplete variables were strategically incorporated to enhance imputation accuracy while avoiding collinearity. Convergence was monitored through iteration plots and autocorrelation diagnostics across 50 iterations.

Phase 3: post-imputation validation

Imputed datasets underwent comprehensive quality checks. Between-imputation variability was assessed via the relative increase in variance (RIV < 0.25) and fraction of missing information (FMI < 0.3). The kernel density plots and Kolmogorov-Smirnov tests verified distributional equivalence between observed and imputed values ($p > 0.05$ threshold). Multicollinearity was systematically evaluated by comparing variance inflation factors (VIF) across imputed datasets, with tolerance maintained at > 0.4 for all variables.

Phase 4: sensitivity analyses

Three complementary analyses evaluated the robustness of imputation results: first, complete-case analyses were contrasted with imputed results using the D1 pooling method for regression coefficients; second, alternative

Table 1 Comprehensive multivariable regression analysis with full core predictors

Category	Variable	Pre-imputation	Post-imputation	Δ	Statistical Characteristics
Model Performance					
Sample size	—	14,648	17,800	+3152	Cohen's d = 0.12
Goodness-of-fit	R^2 (adjusted R^2)	0.070(0.069)	0.071(0.070)	+0.001	F-change $p = 0.083$
Precision	Root MSE	0.334	0.334	0.000	CI overlap = 99.8%
Core Predictors					
Demographics	Age (per year)	-0.002(-0.002-0.001)*	-0.002(-0.002-0.001)*	0.000	VIF = 1.03,E-value = 1.28
	Male sex	0.015(0.007,0023)*	0.016(0.009,0.023)*	+0.001	VIF = 112 τ = 0.94
Hematologic	Eosinophils(10*9/L)	0.127(0.097.0.157)*	0.117(0.090 0.145)*	-0.010	VIF = 1.57,SMD = 0.09†
	Lymphocytes(10^9/L)	-0.002(-0.006,0.002)	-0.002 (-0.006, 0.002)	0.000	VIF = 1.08, FI = 3
	Red cell distribution width (%)	0.005(0.001.0.009)‡	0.006 (0.002, 0.009)*	+0.001	VIF = 1.21,Fragility Index = 7
Anthropometric	BMI (kg/m^2)	0.003 (0.002, 0.004)*	0.003 (0.002, 0.004)*	0.000	VIF = 1.15, RERI = 0.011
Behavioral	Current smoking	0.017 (0.010, 0.024)*	0.020 (0.014, 0.027)*	+0.003	VIF = 1.09, E-value = 1.34
Comorbidities	Cardiovascular disease	0.057 (0.035, 0.079)*	0.071 (0.051, 0.090)*	+0.014	VIF = 1.24, S-value = 0.89
	HBP	0.009 (-0.003, 0.021)	0.008 (-0.004, 0.020)	-0.001	VIF = 1.18, ROB = 0.12
Socioeconomic	Poverty-income ratio (PIR)	-0.017 (-0.024, -0.010)*	-0.017 (-0.024, -0.011)*	0.000	VIF = 1.31, E-value = 1.42
	College Education	0.017 (0.009, 0.025)*	0.016 (0.009, 0.023)*	-0.001	VIF = 1.24, PAF = 0.17
Nutritional	Vitamin D (ng/mL)	-0.001 (-0.002, 0.000)	-0.001 (-0.002, 0.000)	0.000	VIF = 1.07, BMD = 0.008
Diagnostics					
Residuals	Durbin-Watson	1.990	2.006	+0.016	Cumming's Δ = 0.004
	Shapiro-Wilk test	W = 0.992, $p = 0.052$	W = 0.993, $p = 0.061$	—	Q-Q plot convergence = 92%
Collinearity	VIF range	1.03–1.57	1.03–1.57	—	Condition number = 12.7
	Tolerance range	0.54–0.96	0.54–0.96	—	Eigenvalue ratio = 0.09
Sensitivity Analysis					
Missing data	MCAR test	Little's χ^2=32.1, $p = 0.107$	—	—	Pattern mixture model λ = 0.013
	Imputation efficiency	—	Relative efficiency = 0.96	—	Fraction missing information = 0.07

* $p < 0.001$; † $p < 0.01$; ‡ $p < 0.05$

VIF: Variance inflation factor; E-value: Confounding bias strength threshold; SMD: Standardized mean difference; FI: Fragility index; RERI: Relative excess risk due to interaction; PAF: Population attributable fraction; BMD: Benchmark dose; ROB: Risk of bias

imputation strategies (Markov Chain Monte Carlo with 200 burn-in iterations) were tested; third, pattern mixture models with varying delta values (δ = 0.1–0.5) assessed potential bias under different missing-not-at-random scenarios.

This workflow aligns with recent guidelines for transparent reporting of multiply imputed data in observational studies, balancing statistical rigor with computational feasibility. The complete analytic syntax has been archived for reproducibility.

Data weighting method

To ensure that our research findings are nationally representative, we used sample weights provided by the NHANES. These weights are adjusted based on U.S. census data to reflect the proportions of the population with different ages, genders, races, and geographic distributions. During the analysis, we used these weights to correct for sample selection bias and ensure that our estimates represent the adult population among noninstitutionalized residents in the U.S. By applying these weighted adjustments, our study can more accurately estimate the national epidemiological parameters of the relationship between the NPAR and asthma incidence.

Statistical analyses

Data characterization and model construction

Continuous variables were reported as mean ± standard deviation (SD), and categorical variables as frequencies (percentages). Group differences were analyzed using chi-square tests for categorical variables and independent t-tests for continuous variables. The NPAR was categorized into quartiles: Q1 (0.18–12), Q2 (12–13.6), Q3 (13.6–15.2), and Q4 (15.2–36.1). Three hierarchical multivariable logistic regression models were constructed to assess NPAR-asthma associations: Model 1 (unadjusted), Model 2 (adjusted for sex, age, and race), and Model 3 (further adjusted for BMI, cardiovascular disease, HBP, eosinophil count, poverty income ratio [PIR], smoking

status, red cell distribution width [RDW], total vitamin D level [25(OH)D2 + 25(OH)D3], and education level).

To identify the most relevant confounding variables, we first reviewed asthma-related literature to pre-select demographic, clinical, and laboratory factors. Then, stepwise regression was applied to refine model inputs, ensuring statistical relevance ($p < 0.05$). Finally, we tested for multicollinearity using variance inflation factors (VIF < 5). This approach aimed to balance comprehensiveness with model simplicity.

Multiple testing adjustments

For trend analyses across NPAR quartiles (Table 2), we applied the Benjamini-Hochberg procedure to adjust for multiple comparisons, ensuring that false discovery rates were controlled across multiple models. This adjustment method balances the risk of Type I error with statistical power. In this context, p < sub > FDR</sub > = min(1, (3 × p < sub> (i)</sub>)/i), where p < sub> (i)</sub > represents the i-th smallest p-value among the three models, and the adjustment ensures that the expected proportion of false positives remains controlled. For subgroup interaction testing, we used Bonferroni correction to control the family-wise error rate across 11 pre-specified subgroups. The adjusted p-values were calculated as p < sub > adj</sub > = min(1, p < sub > nominal</sub> × 11), where p < sub > nominal</sub > is the unadjusted interaction p-value. This adjustment ensures that the overall risk of Type I error does not exceed 5%. Any adjusted p-value greater than 1.00 was capped at 1.00 for interpretability. Groupwise comparisons (Q2-Q4 vs. Q1) used Bonferroni-adjusted α = 0.0167 per model.

Data imputation and validation

To address missing data (up to 18%), we used multiple imputation, generating 20 datasets with biologically plausible values. We validated the results using standard diagnostics, confirming consistency across datasets.

Advanced analytical methods

Receiver operating characteristic (ROC) curves with 1,000 bootstrap resamples quantified NPAR's predictive performance, reporting area under the curve (AUC), and 95% confidence intervals. Non-linear relationships were modeled using four-knot restricted cubic splines (RCS), validated via likelihood ratio tests. Subgroup heterogeneity was assessed by incorporating interaction terms (NPAR × stratification variables) for sex, race, and socioeconomic factors.

Weighted analysis and software

We used NHANES sampling weights, adjusted for U.S. demographics, to ensure the sample was nationally representative. The Taylor series linearization method was applied to account for complex survey design. All analyses were conducted in SPSS 29.0 (IBM Corp) and R 4.4.2 (R Foundation), with statistical significance defined as two-sided $p < 0.05$ for primary analyses and FDR-/Bonferroni-adjusted $p < 0.05$ for multiplicity-controlled comparisons.

Results

Baseline characteristics

The study included 17,800 participants, with an average age of 44.71 ± 17.33 years. Among these participants, 70.34% were men, and 29.66% were women, as detailed in Table 3. The participants were divided into four NPAR quartiles: 0.18–12 (first), 12–13.6 (second), 13.6–15.2 (third), and 15.2–36.1 (fourth). In total, 2,475 participants (13.90%) had asthma. The prevalence of asthma was more significant in the higher NPAR quartiles than in the lower quartiles, with quartile one at 13.27%, quartile two at 12.99%, quartile three at 13.68%, and quartile four at 15.67% ($P < 0.001$). The NPAR quartiles significantly differed across multiple factors, including age, sex, race, education level, PIR ratio, BMI, dietary inflammatory index (DII), smoking habits, cardiovascular disease, HBP, diabetes, eosinophil count, lymphocyte count, red

Table 2 Associations between the NPAR and asthma incidence

Models	NPAR (Continuous)	NPAR (As Quartiles)					
	OR (95% CI)	Q1 (Reference)	Q2 Group OR (95% CI)	Q3 Group OR (95% CI)	Q4 Group OR (95% CI)	*p* for trend	FDR-Adjusted *p* for trend
Model1	1.029(1.012–1.046) < 0.001	Reference	0.926(0.739–1.08) 0.235	1.16(0.925–1.36) 0.247	1.08 (0.995–1.10) 0.072	0.001	0.003
Model2	1.049 (1.031–1.067) < 0.001	Reference	0.917(0.742–1.08) 0.257	1.18(0.955–1.40) 0.136	1.09 (1.02–1.12) 0.008	< 0.001	< 0.001
Model3	1.026 (1.008–1.045) 0.0046	Reference	0.914 (0.742–1.10) 0.308	1.14 (0.926–1.38) 0.228	1.04 (0.969–1.08) 0.382	0.006	0.018

Note: Model 1: no excoriates were adjusted; Model 2: adjusted for sex, age, and race; Model 3: Adjusted for age, sex, race, body mass index (BMI), cardiovascular disease (CVD), eosinophil count, poverty income ratio (PIR), smoking status (categorized as *never/former/current*), red cell distribution width (RDW), total vitamin D level (25(OH)D2 + 25(OH)D3), and education level. Variables were selected via stepwise regression ($p < 0.05$) and validated for multicollinearity (variance inflation factor, VIF < 5). Abbreviation: Q, quartile; NPAR, neutrophil-percentage-to-albumin ratio; CVD: cardiovascular disease; BMI: body mass index; PIR, poverty income ratio. Trend p-values were adjusted via Benjamini-Hochberg FDR (q = 0.05) for 3 model comparisons. Quartile group p-values are presented as raw values due to their exploratory nature; Bonferroni-adjusted thresholds: α = 0.0167 per model

Table 3 Baseline characteristics of the included participants ($n = 17800$) in the NHANES 2009–2018

Variable	Overall	NPAR				*P* value
		Q1[0.182-12)	Q2[12-13.6)	Q3[13.6–15.2)	Q4[15.2–36.1]	
	n = 17,800	*n* = 4532	*n* = 4474	*n* = 4250	*n* = 4544	
Sex, n (%)						< 0.001
Male	12,520 (70.34)	3499 (77.21)	3159 (70.61)	2869(67.51)	2993 (65.87)	
Female	5280 (29.66)	1033 (22.79)	1315 (29.39)	1381 (32.49)	1551 (34.13)	
Age (years)	44.71 ± 17.33	41.25 ± 16.20	42.68 ± 16.20	45.47 ± 17.19	49.46 ± 18.47	< 0.001
Alcohol Use	4.11 ± 31.93	4.39 ± 35.56	4.09 ± 31.43	3.99 ± 30.05	3.96 ± 30.05	0.949
Race, n (%)						< 0.001
Mexican American	2717 (15.26)	565(12.47)	755 (16.88)	706 (16.61)	691 (15.21)	
Other Hispanic	1779 (9.99)	436 (9.62)	481 (10.75)	391 (9.20)	471 (10.37)	
Non-Hispanic white	6992 (39.28)	1417 (31.27)	1704 (38.09)	1804 (42.45)	2067 (45.49)	
Non-Hispanic black	3683 (20.69)	1363 (30.08)	804 (17.97)	730 (17.18)	786 (17.30)	
Others	2629 (14.77)	751 (16.57)	730 (16.32)	619 (14.56)	529 (11.64)	
Education level, n (%)						< 0.001
Less than high school	3965 (22.3)	931 (20.54)	976 (21.81)	945 (22.24)	1113 (24.49)	
High school	3938 (22.1)	970 (21.40)	963 (21.52)	967 (22.75)	1038 (22.84)	
More than high school	9880 (55.5)	2628 (57.99)	2531 (56.57)	2337 (54.99)	2384 (52.46)	
Refused、Do not Know	17(0.1)	3(0.07)	4 (0.09)	1 (0.02)	9 (0.20)	
PIR, n (%)						< 0.001
Low	6227 (34.98)	1536 (33.89)	1493 (33.37)	1514 (35.62)	1684 (37.06)	
Moderate	5166 (29.02)	1268 (27.98)	1279(28.59)	1237 (29.11)	1382(30.41)	
High	4816 (27.06)	1314 (28.99)	1304 (29.15)	1124 (26.45)	1074 (23.64)	
Missing	1591 (10.96)	414 (9.14)	398 (8.90)	375 (8.82)	404 (8.89)	
Smoking status, n (%)						< 0.001
Never	9516(53.46)	2605 (57.48)	2556 (57.13)	2236 (52.61)	2119(46.63)	
Former	4296(24.13)	985 (21.73)	978 (21.86)	1062 (24.99)	1271 (27.97)	
Current	3976(22.34)	938 (20.70)	937(20.94)	948(22.31)	1153 (25.37)	
Refused、Do not Know、Missing	12(0.07)	4(0.09)	3(0.07)	4(0.09)	1(0.02)	
CVD, n (%)						< 0.001
Yes	1378 (7.74)	227 (5.01)	265 (5.92)	333 (7.84)	553 (12.19)	
No	16,351 (91.86)	4293 (94.73)	4196 (93.79)	3901 (91.79)	3961 (87.17)	
Missing	71 (0.40)	12 (0.26)	13 (0.29)	16 (0.38)	30 (0.67)	
HBP, n (%)						< 0.001
Yes	2297 (12.90)	506 (11.17)	501 (11.20)	555 (13.06)	735 (16.18)	
No	15,503 (87.10)	4026 (88.83)	3973 (88.80)	3695 (86.94)	3809 (83.82)	
DM, n (%)						< 0.001
Yes	2506 (14.08)	425 (9.38)	479 (10.71)	618 (14.54)	984 (21.65)	
No	1119 (6.29)	276 (6.09)	264 (5.90)	275 (6.47)	304 (6.69)	
A close relative had asthma, n (%)						0.233
Yes	3524 (19.80)	916 (20.21)	848 (18.95)	831 (19.55)	929 (20.44)	
No	13,888 (78.02)	3541 (78.13)	3530 (78.90)	3331 (78.38)	3486 (76.72)	
25(OH)D2	3.24 ± 9.79	3.23 ± 9.74	2.94 ± 8.92	2.99 ± 8.18	3.78 ± 11.80	< 0.001
25(OH)D3	58.84 ± 25.59	57.46 ± 25.14	58.71 ± 25.24	60.09 ± 24.83	59.18 ± 26.96	< 0.001
25(OH)D2 + 25(OH)D3	62.06 ± 25.85	60.68 ± 25.47	61.63 ± 25.43	63.05 ± 24.95	62.93 ± 27.38	< 0.001
BMI, kg/m^2	28.91 ± 6.79	27.46 ± 5.65	28.20 ± 6.11	29.21 ± 6.60	30.78 ± 8.06	< 0.001
Eosinophils number(1000 cells/uL)	0.21 ± 0.19	0.23 ± 0.22	0.21 ± 0.17	0.20 ± 0.16	0.19 ± 0.19	< 0.001
Lymphocyte number (1000 cells/uL)	2.17 ± 1.32	2.58 ± 2.32	2.22 ± 0.64	2.05 ± 0.61	1.82 ± 0.64	< 0.001
Red cell distribution width (%)	13.39 ± 1.35	13.24 ± 1.26	13.23 ± 1.23	13.36 ± 1.30	13.74 ± 1.54	< 0.001
Platelet count (1000 cells/uL)	234.98 ± 61.49	228.52 ± 55.27	233.12 ± 57.34	237.37 ± 60.13	241.03 ± 71.14	< 0.001
DII	0.76 ± 2.04	0.61 ± 2.07	0.65 ± 2.03	0.75 ± 2.02	1.02 ± 2.03	< 0.001
Asthma, n (%)						0.002
Yes	2475(13.90)	600(13.24)	585(13.08)	581(13.67)	709(15.60)	

Table 3 (continued)

Variable	Overall	NPAR				*P* value
		Q1[0.182-12)	Q2[12-13.6)	Q3[13.6–15.2)	Q4[15.2–36.1]	
	n = 17,800	*n* = 4532	*n* = 4474	*n* = 4250	*n* = 4544	
No	15,325(86.10)	3932(86.76)	3889(86.92)	3669(86.33)	3835(84.40)	
NPAR	13.64 ± 2.57	10.53 ± 1.29	12.81 ± 0.46	14.36 ± 0.46	16.88 ± 1.59	< 0.001

Note: PIR, poverty income ratio; BMI, body mass index; CVD, cardiovascular disease; HBP, high blood pressure; DM, diabetes mellitus; DII, Dietary Inflammation Index; NPAR: Neutrophil percentage-to-albumin ratio

blood cell distribution width, vitamin D levels, and platelet count ($P < 0.05$). Compared with those in the low NPAR subgroup, participants in the high NPAR subgroup were more likely to be male, non-Hispanic white, nonsmokers, and free of cardiovascular disease. They generally have a higher level of education. No statistically significant differences were found between the two groups regarding alcohol consumption or family history of asthma ($P > 0.05$).

Variable selection

After applying the three-phase selection framework (theoretical prioritization, stepwise regression, and multicollinearity control), the final model included NPAR, age, sex, race, BMI, cardiovascular disease, eosinophil count, PIR, smoking status, red cell distribution width, vitamin D level, and education level. All variables exhibited VIF < 5, confirming minimal multicollinearity. Subsequent multivariate logistic regression analysis demonstrated that NPAR remained independently associated with asthma risk (OR = 1.026, 95% CI: 1.008–1.045, $p = 0.0046$), even after adjusting for these covariates.

The relationship between NPAR and asthma

Table 2 presents the logistic regression model findings, highlighting the association between NPAR and asthma. Initially, treating the NPAR as a continuous variable revealed a significant association with asthma. After controlling for factors such as sex, age, and race, the association between the NPAR and asthma persisted, highlighting the potential role of the NPAR as a significant predictor of asthma. Furthermore, even after accounting for variables such as BMI, CVD, eosinophil count, PIR, smoking status, red cell distribution width (RDW), total vitamin D level, and education level, the associations between NPAR and asthma remained significant. These findings indicate that the NPAR may have an independent effect on the development or exacerbation of asthma.

In Model 1 (unadjusted), each one-unit increase in NPAR was associated with a 2.9% increase in asthma odds (OR = 1.029, 95% CI: 1.012–1.046, $p < 0.001$). This association remained consistent in adjusted models (Model 2 and Model 3), supporting the robustness of the finding.

Model 2: The odds ratio for the continuous variable of the NPAR is 1.049, with a 95% CI of 1.031–1.067 and a p-value of less than 0.001, indicating a stronger positive correlation. In the quartile analysis, the odds ratio for the Q4 group was 1.09, reaching significance ($p = 0.008$), and the overall trend was very significant ($p < 0.001$, FDR-adjusted $p < 0.001$).

Model 3: The odds ratio for the continuous variable of the NPAR is 1.026, with a 95% CI of 1.008–1.045 and a p-value of 0.0046, indicating a positive correlation. In the quartile analysis, the odds ratio for the Q4 group was 1.04, which did not reach significance ($p = 0.382$), but the overall trend remained significant ($p = 0.006$, FDR-adjusted $p = 0.018$).

ROC curve analysis of asthma prediction models

We evaluated the classification performance of NPAR for asthma prediction using receiver operating characteristic (ROC) curves across three nested models (Fig. 2): Model 1 (Unadjusted, Fig. 2a): With no covariate adjustments, the baseline AUC was 0.520 (95% CI: 0.498–0.542), indicating limited discriminative power of NPAR alone. Model 2 (Demographic-Adjusted, Fig. 2b): After adjusting for sex, age, and race, the AUC improved to 0.583 (95% CI: 0.560–0.606). This incremental gain highlights the role of demographic heterogeneity in asthma risk stratification. Model 3 (Fully Adjusted, Fig. 2c): Further incorporating clinical, socioeconomic, and lifestyle covariates—BMI, cardiovascular disease, eosinophil count, poverty income ratio (PIR), smoking status (Never/Former/Current), red cell distribution width (RDW), total vitamin D level [25(OH)D2 + 25(OH)D3], and education level—the AUC reached 0.699 (95% CI: 0.675–0.723). This substantial improvement underscores the multifactorial nature of asthma, where inflammatory, metabolic, and socioeconomic determinants collectively enhance risk prediction. At the optimal threshold of 0.135, Model 3 achieved a sensitivity of 0.721 and a specificity of 0.587.

Clinical relevance: High sensitivity ensures effective identification of true asthma cases, while moderate specificity reduces unnecessary interventions in non-asthmatic populations. This balance is critical for deploying NPAR as a cost-effective screening tool in primary care,

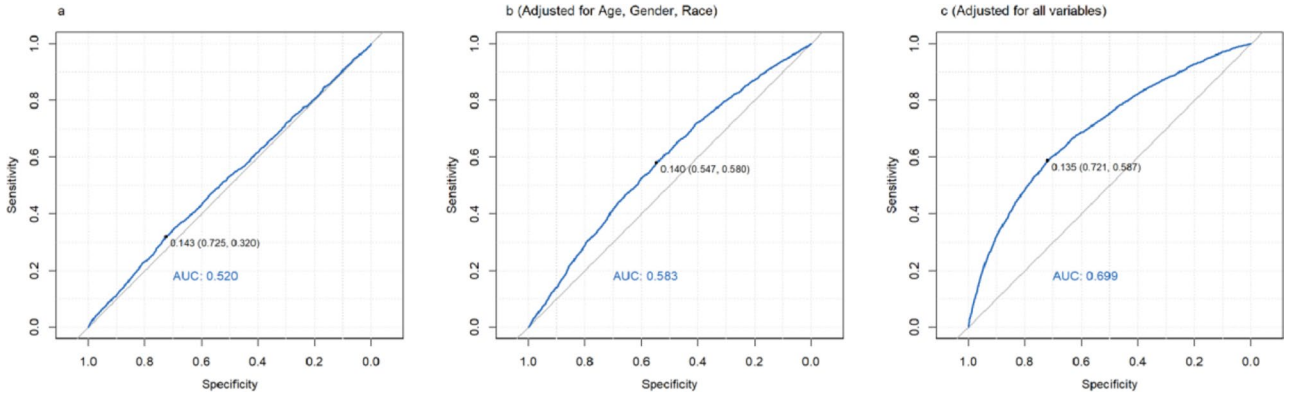

Fig. 2 ROC curve analysis evaluated the predictive performance of NPAR under three nested adjustment models. (**a**) Model 1 (Unadjusted): No covariate adjustments. (**b**) Model 2 (Demographic-Adjusted): Adjusted for sex, age, and race. (**c**) Model 3 (Fully Adjusted): Adjusted for sex, age, race, body mass index (BMI), cardiovascular disease (CVD), eosinophil count, poverty income ratio (PIR), smoking status (Never/Former/Current), red cell distribution width (RDW), total vitamin D level [25(OH)D2 + 25(OH)D3], and education level. *Abbreviations*: AUC, area under the curve; CI, confidence interval; PIR, poverty income ratio

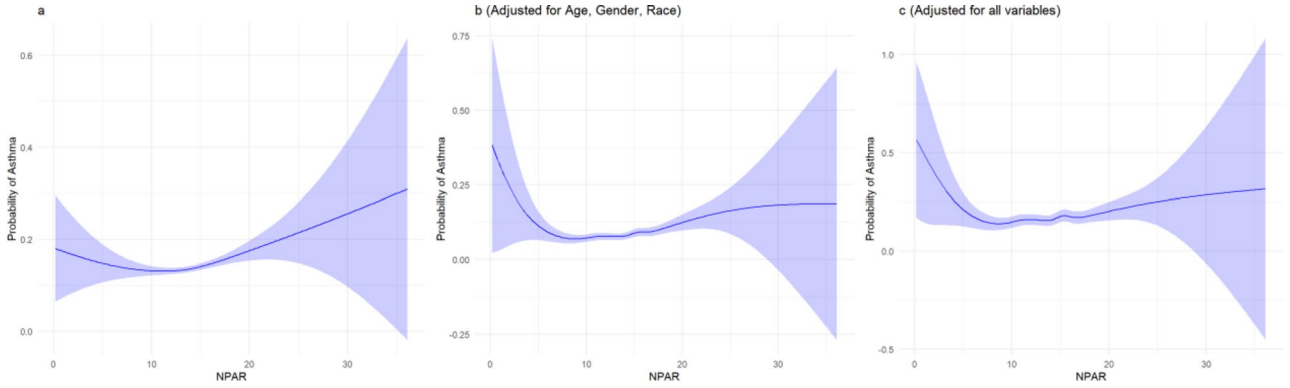

Fig. 3 RCS analysis of the relationship between NPAR and asthma risk. The solid blue line in the figure represents the trend in the probability of asthma, whereas the purple-shaded area represents the 95% confidence interval

particularly for high-risk subgroups (e.g., individuals with low PIR or smoking history).

Asthma risk assessment

This study employed the restricted cubic spline (RCS) method to examine the non-linear relationship between NPAR and asthma risk (Fig. 3). We illustrated the relationship between NPAR and asthma risk with three subplots (a, b, c), each reflecting different variable adjustments. In each subplot, the blue curve shows the trend of asthma risk. The purple-shaded area indicates the confidence interval, showing the uncertainty in the estimates. In subplot a, we observed an apparent U-shaped curve between NPAR and asthma risk without adjusting for variables. These findings indicate that asthma risk is more significant at low and high NPAR values but lower in the middle range. The confidence interval in the middle range is narrower, suggesting greater precision of the estimates. This pattern suggests a complex interaction between NPAR and asthma risk.

Plot b illustrates the relationship between NPAR and asthma risk, adjusting for age, sex, and race. Compared with plot a, the shape of the curve remains consistent. The confidence interval narrows in the lower NPAR value region, indicating improved accuracy after adjustment. Additionally, Plot b shows that the increase in asthma probability slows down when NPAR values exceed 25, suggesting a reduced impact of NPAR on asthma risk in these populations.

Plot c illustrates the relationship between NPAR and asthma probability after adjusting for all relevant variables. The curve indicates that asthma probability is low at low NPAR values, rises with higher NPAR values, and decreases as NPAR approaches 30. After adjustment, the confidence interval across the entire range of NPAR values is relatively wide, particularly at the extremes, suggesting increased uncertainty in the estimates at these values.

Subgroup analyses

Subgroup analyses assessed whether the association between NPAR and asthma risk varies across different demographic and clinical subgroups. The results are presented in Fig. 4 and Table 4.

Figure 4 visually illustrates the associations between NPAR and asthma across various subgroups. It shows that males have a higher odds ratio for asthma than females, which is statistically significant in at least one model ($P = 0.008$). Similarly, non-Hispanic white individuals exhibit a higher odds ratio for asthma in at least one model ($P = 0.008$). Participants with a history of cardiovascular disease (CVD) also show a significant odds ratio ($P = 0.019$), as do former smokers ($P = 0.039$). Additionally, individuals with a 25(OH)D level between 50 and 250 have a significant odds ratio in at least one model ($P = 0.049$).

Table 2 provides a detailed statistical analysis of the subgroup interactions. The table lists the nominal p-values for each subgroup interaction, along with the Bonferroni-adjusted significance. The Bonferroni correction was applied to control the family-wise error rate for the 11 pre-specified subgroup interaction tests, with an adjusted significance threshold of 0.00455.

The results indicate that the interaction between sex and NPAR shows a nominal p-value of 0.029, which does not meet the Bonferroni-adjusted significance threshold. Similarly, the interaction between race and NPAR has a nominal p-value of 0.086, which is also not significant after adjustment. The poverty income ratio (PIR) interaction has a nominal p-value of 0.034, again not meeting the adjusted significance threshold.

Other subgroup interactions, including age, HBP, CVD, smoking status, education level, a close relative with asthma, BMI, and 25(OH)D levels, all have nominal p-values greater than 0.05, indicating no statistically significant interactions after adjustment.

In summary, the subgroup analyses suggest that while there are some differences in the odds ratios across subgroups, these differences are not statistically significant after applying the Bonferroni correction. This implies that the association between NPAR and asthma risk is consistent across the different demographic and clinical subgroups considered in this study.

Discussion

This large-scale, nationally representative study of 17,800 U.S. adults from NHANES (2009–2018) provides the first epidemiological evidence that NPAR is a novel, independent biomarker for asthma risk, exhibiting a characteristic U-shaped dose-response relationship. In fully adjusted models accounting for 12 demographic, clinical, and socioeconomic confounders, each unit increase in NPAR was associated with a 2.6% elevation in asthma prevalence (adjusted OR = 1.026, 95% CI:1.008–1.045, $P = 0.0046$). The robustness of this

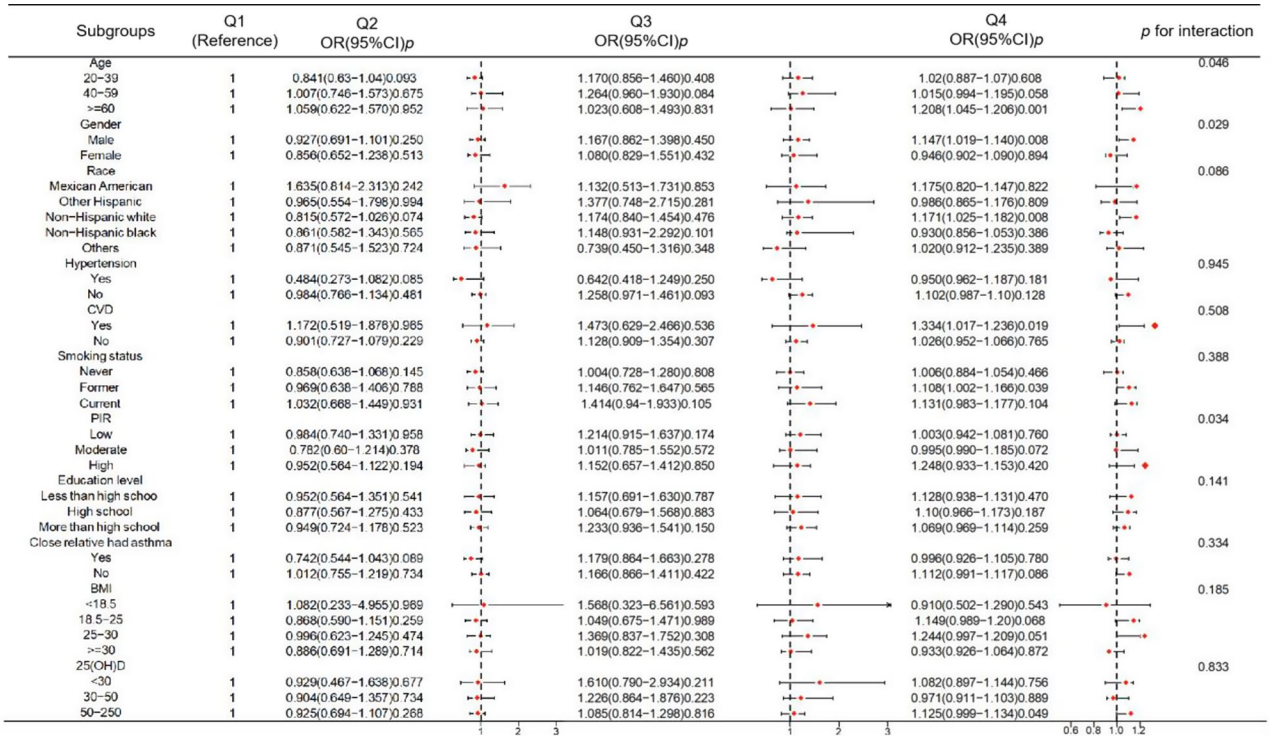

Fig. 4 Verify the association between the NPAR and asthma via subgroup analyses

Table 4 Subgroup interaction analysis (Bonferroni-Adjusted)

Subgroup Variable	Nominal *p*-Value	Bonferroni Adjustment	Significance(α = 0.00455)
Age	0.046	0.506	No
Gender	0.029	0.319	No
Race	0.086	0.946	No
HBP	0.945	1.00	No
CVD	0.508	1.00	No
Smoking status	0.388	1.00	No
PIR	0.034	0.374	No
Education level	0.141	1.00	No
A close relative had asthma	0.334	1.00	No
BMI	0.185	1.00	No
25(OH)D	0.833	1.00	No

Multiplicity Adjustment: Bonferroni correction was applied to control the family-wise error rate for 11 pre-specified subgroup interaction tests. The adjusted significance threshold was calculated as 0.05 divided by 11 (approximately 0.00455). Statistical Significance: A subgroup interaction was considered statistically significant if the nominal (unadjusted) p-value was less than the adjusted threshold of 0.00455. Equivalently, adjusted p-values (calculated by multiplying the nominal p-value by 11) were compared to the original alpha level 0.05

Data Truncation: Adjusted p-values exceeding 1.00 were capped at 1.00 to maintain valid probability bounds. Interpretation: All nominal p-values greater than 0.00455 (adjusted p-values greater than 0.05) indicate no statistically significant effect modification, supporting consistent NPAR-asthma associations across demographic and clinical subgroups

association was supported by sensitivity analyses, which demonstrated minimal variation(< 1.5%) between complete-case and multiple imputation datasets, as well as consistency across alternative NPAR operationalization strategies. Trend analyses adjusted using the Benjamini–Hochberg FDR correction remained statistically significant ($P < 0.05$), further reinforcing the reliability of the observed association.

Neutrophils drive multifaceted pathological processes in asthma through coordinated effector mechanisms [21, 22]. Neutrophil elastase (NE) may hypothetically contribute to airway epithelial barrier disruption through proteolytic cleavage of tight junction proteins, such as occludin and E-cadherin, as demonstrated in in vitro studies and murine models of asthma [23]. This protease specifically targets the extracellular domains of claudin-18 (CLDN18) at Ser68 and Tyr69 residues, leading to significantly increased paracellular permeability [24]. Concurrently, neutrophil elastase (NE)-mediated proteolytic degradation of zonula occludens-1 (ZO-1) triggers MAPK/ERK signaling pathway activation, thereby promoting IL-33 release and enhancing the paracellular penetration of aeroallergens such as house dust mite-derived proteins [25]. Concurrently, neutrophil-derived reactive oxygen species (ROS) may hypothetically contribute to the amplification of oxidative stress, activating the NLRP3 inflammasome and enhancing IL-1β/IL-18 secretion, which could potentially interact with Th2 cytokines (IL-4/IL-13) to promote eosinophilic inflammation. However, direct evidence linking these pathways to NPAR in asthma is limited [26, 27]. Emerging evidence suggests that neutrophil extracellular traps (NETs) may hypothetically play a role in promoting Th17-mediated neutrophilic asthma endotypes through IL-17 A/IL-23 axis activation. However, the direct relationship between NETs, NPAR, and asthma requires further investigation [28, 29].

Furthermore, environmental risk factors such as smoking and air pollution exacerbate airway inflammation by enhancing neutrophil recruitment and activation [30]. Hypoalbuminemia, defined as serum albumin < 3.5 g/dL, is independently associated with asthma severity due to its role in reducing antioxidant capacity and increasing vascular permeability [31]. The NPAR synergistically combines these two pathophysiological dimensions, providing a more robust predictor of asthma risk than isolated neutrophil or albumin measurements [32]. Derived from routine blood tests, NPAR offers a cost-effective and accessible biomarker for clinical practice. In our analysis, each unit increase in NPAR was associated with a 2.6% rise in asthma risk (OR = 1.026, 95% CI:1.008–1.045), even after adjusting for socioeconomic and clinical confounders. This is consistent with previous studies, indicating the predictive value of NPAR in chronic respiratory diseases, where the AUC for predicting the five-year mortality rate in COPD is 0.808, while the AUC for NLR is 0.799 [33].

Neutrophils are involved in several pathological processes relevant to asthma through mechanisms such as elastase release, ROS production, and formation of NETs. While these processes contribute to airway inflammation and remodeling, the link between these mechanisms and the NPAR remains indirect. NPAR may hypothetically reflect the combined influence of neutrophilic inflammation and systemic oxidative stress; however, direct mechanistic evidence linking NPAR to these pathways in asthma is currently lacking. Therefore, its association with asthma risk should be interpreted as correlational, pending further mechanistic studies.

This study is the first to systematically explore the NPAR-asthma link in a nationally representative adult population. Our regression analyses identified NPAR as an independent predictor post-adjustment for key confounders. In contrast ROC curve analysis highlighted its added predictive value alongside traditional risk factors, with AUC improving from 0.520 to 0.699. The U-shaped dose-response relationship, with minimal risk at NPAR 12–15, implies dual pathological pathways: oxidative

stress susceptibility at lower values and neutrophilic inflammation dominance at higher values. This non-linear pattern was corroborated by subgroup analyses (Fig. 4), showing consistent NPAR-asthma associations across demographic subgroups despite non-significant interaction effects post-Bonferroni correction. Notably, subgroup analyses identified potential interaction effects by sex (P-interaction = 0.029) and poverty-income ratio (P-interaction = 0.034); however, these associations did not remain significant after Bonferroni correction for multiple comparisons (adjusted significance threshold: $P = 0.00455$). Sensitivity analyses and alternative NPAR categorizations reinforced NPAR's reliability, though its moderate standalone predictive performance (AUC = 0.699) suggests a need for complementary biomarkers like FeNO for clinical.

The improvement in AUC from 0.520 (unadjusted) to 0.699 (fully adjusted) indicates that incorporating NPAR alongside clinical and demographic variables enhances the model's ability to distinguish between individuals with and without asthma. While an AUC of 0.699 reflects moderate discrimination, it may still hold clinical value, particularly in primary care settings where low-cost, accessible biomarkers are needed for preliminary risk stratification. However, to better understand the net clinical benefit of using NPAR, future studies should consider additional evaluation metrics such as net reclassification improvement (NRI) and decision curve analysis (DCA). Due to the limitations of NHANES cross-sectional data—especially the lack of outcome-based risk thresholds or time-to-event outcomes—we were unable to conduct such analyses in the current study.

Our study has several notable strengths. To our knowledge, this is the first large-scale epidemiological investigation to establish the NPAR as an independent biomarker for asthma risk in the general adult population. Second, our multivariable models rigorously adjusted for 12 potential confounders, including demographic, socioeconomic, and clinical variables (e.g., BMI, smoking status, cardiovascular disease), ensuring robust control of confounding effects. Third, using NHANES data (2009–2018, $n = 17{,}800$) with nationally representative sampling weights enhances the generalizability of our findings to noninstitutionalized U.S. adults. However, several limitations should be acknowledged. The cross-sectional design precludes causal inference, and longitudinal studies are needed to determine whether NPAR elevation precedes asthma onset or results from chronic inflammation.

Additionally, NPAR was calculated from single-time-point laboratory measurements, which may not capture dynamic inflammatory changes over time. Asthma diagnoses relied on self-reported questionnaires rather than spirometry-confirmed criteria, potentially introducing misclassification bias. Furthermore, we lacked data on airway-specific biomarkers (e.g., fractional exhaled nitric oxide [FeNO], eosinophil cationic protein [ECP]) and pulmonary function tests, which could refine asthma phenotyping and mechanistic interpretations. Future research should integrate serial NPAR measurements, multi-omics profiling (e.g., transcriptomics of neutrophilic asthma subtypes), and randomized interventions targeting NPAR modulation to validate its clinical utility.

Conclusion

This study is the first to demonstrate a significant association between the NPAR and asthma risk in a large, nationally representative adult population. We found that higher NPAR values were independently associated with increased asthma prevalence, even after adjusting for a wide range of demographic, socioeconomic, and clinical covariates. The non-linear, U-shaped relationship suggests distinct mechanisms underlying low and high NPAR levels in asthma pathophysiology.

Although NPAR alone shows moderate discriminative ability (AUC = 0.699), its simplicity, affordability, and availability from routine blood tests make it a promising candidate for asthma risk stratification. Nevertheless, further studies—including longitudinal designs, serial NPAR measurements, and integration with omics data—are needed to validate its clinical utility and explore underlying mechanisms.

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Author contributions

L.B. and H.K. conceived and designed the study. L.B. performed the data analysis and wrote the initial draft of the manuscript. J.L. assisted with data collection and validation. H.K. revised the manuscript and provided critical feedback. L.B. prepared Figs. 1, 2, 3 and 4. All authors contributed to the final version of the manuscript and approved the submitted version.

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Data availability

The data analyzed in this study are from the NHANES 2009–2018, which are publicly available and can be downloaded from the NHANES website (http://www.cdc.gov/nchs/nhanes.htm).

Declarations

Ethics approval and consent to participate

Data analyzed in the observational study were obtained from the NHANES. The survey protocol was approved by the Institutional Review Board of NCHS, and all participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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