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Association of eosinophil-to-monocyte ratio with asthma exacerbations in adults: a cross-sectional analysis of NHANES data

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Abstract

Background The eosinophil-to-monocyte ratio (EMR) has emerged as a promising biomarker for assessing inflammation in various diseases, and this study aims to investigate its potential in predicting asthma exacerbations.

Methods This cross-sectional study used data from the National Health and Nutrition Examination Survey (NHANES) 1999–2020. A total of 4,738 adults were included in the analysis, and weighted analyses were performed to ensure a representative sample of the general population. The relationship between EMR and asthma exacerbation risk was assessed using multivariable logistic regression with progressively adjusted covariates across multiple models. Subgroup analyses were performed by stratifying key covariates to explore interactions. Restricted cubic spline (RCS) analysis was applied to evaluate non-linear relationships. Sensitivity analyses confirmed the robustness and reliability of the results.

Results Elevated EMR levels were significantly associated with an increased risk of asthma exacerbations ($p < 0.001$ in all models). In the highest EMR quartile (Q4), the odds ratio for exacerbation compared to the lowest quartile (Q1) was 1.54 (95% CI: 1.23, 1.93) in Model 1, increasing to 1.56 (95% CI: 1.24, 1.97) in Model 2 and 1.58 (95% CI: 1.24, 2.02) in Model 3, after further adjustments. Subgroup analyses showed consistent associations across various characteristics (all p for interaction > 0.05), while RCS analysis revealed a linear relationship without threshold effects (p for nonlinear > 0.05).

Conclusion EMR demonstrates strong potential as a biomarker for predicting asthma exacerbations, with implications for personalized asthma management.

Keywords Asthma, Eosinophil-to-monocyte ratio (EMR), Exacerbation, Biomarker, NHANES

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Background

Asthma is a widespread chronic inflammatory disorder impacting millions worldwide, characterized by airway inflammation, bronchial hyperreactivity, and reversible airflow obstruction [1]. Eosinophils are crucial in asthma pathophysiology, contributing to airway inflammation and structural remodeling via the release of cytotoxic granules, cytokines, and chemokines [2]. Consequently, blood eosinophil counts are frequently used as biomarkers in asthma management, aiding in the targeted use of corticosteroids and biologic therapies for eosinophilic inflammation [3, 4].

The eosinophil-to-monocyte ratio (EMR) has emerged as a promising biomarker in multiple inflammatory conditions. For example, in community-acquired pneumonia (CAP), low EMR levels correlate with increased in-hospital mortality and severe disease [5]. Similarly, in pulmonary embolism (PE), lower EMR levels predict poor long-term outcomes [6]. In pediatric COVID-19 cases, a reduced EMR can reliably differentiate infected from non-infected children across age groups [7]. Furthermore, reduced EMR values are linked to higher mortality rates in patients with ST-elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention, as well as adverse three-month outcomes following thrombolysis for acute ischemic stroke (AIS) [8, 9]. Elevated EMR levels are also associated with greater disease severity in autoimmune conditions, such as vitiligo [10].

Despite the established role of eosinophils in asthma, EMR's relevance in asthma remains largely unexplored. Investigating the relationship between eosinophils and monocytes could provide insights into asthma severity, disease management, and exacerbation risk. This study aims to assess the potential of EMR as a biomarker in asthma, with a focus on its association with disease severity and exacerbation risk.

Materials and methods

Data source and study population

The National Health and Nutrition Examination Survey (NHANES) is an ongoing, multistage, stratified sampling program that evaluates the health and nutritional status of U.S. adults and children across a broad spectrum of health and nutrition indicators. Its primary objective is to provide a comprehensive profile of the non-institutionalized civilian U.S. population. To ensure representativeness, NHANES employs a complex, multistage probability sampling method. Written informed consent was obtained from all participants, and the study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to uphold rigorous methodological and ethical standards [11]. The study protocols were approved by the Institutional Review Board (IRB) of the National Center for Health Statistics (NCHS) [12].

This cross-sectional study out of an initial cohort of 107,622 participants from eleven NHANES cycles (1999–2020), 92,812 individuals without asthma were excluded, leaving 14,810 participants diagnosed with asthma. Of these, 6,247 were further excluded due to the absence of data on asthma exacerbation, resulting in 9,254 participants with verified exacerbation status. After excluding 3,996 participants under 18 years of age, 5,258 adults aged 18 or older remained. Finally, 520 participants with missing complete blood count (CBC) data were excluded, yielding a final sample of 4,738 participants. The participant selection process is illustrated in Fig. 1.

Definitions of asthma and exacerbation

Asthma status in the NHANES database was identified by asking participants, "Has a doctor or other health professional ever told you that you have asthma?" A "Yes" response classified the participant as having asthma. Those reporting a diagnosis were further asked, "During the past 12 months, have you had an episode of asthma or an asthma attack?" A "Yes" response to this question indicated an asthma exacerbation within the past year. The reliability of self-reported asthma status has been validated in previous studies, supporting the robustness of this method [13–17].

Definition of EMR

CBC were conducted on specimens using the Beckman Coulter MAXM instrument at the Mobile Examination Center (MEC). Blood samples underwent initial screening based on specific exclusion criteria, and NHANES implemented quality control measures throughout both collection and analysis. The white blood cell (WBC) count and its differential components—neutrophils, lymphocytes, monocytes, and eosinophils—were analyzed. The primary variable, EMR, was determined by calculating the ratio of eosinophil to monocyte counts, following established research protocols [5–10].

Covariables assessment

The covariates considered in this study included age, gender, race, marital status, body mass index (BMI), smoking status, glucocorticoid usage, blood cell counts, chronic obstructive respiratory diseases (CORD), hypertension, diabetes, chronic heart failure (CHF), coronary artery disease (CHD), and malignancy. Race was categorized as Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other. Marital status was grouped as married/living with a partner, widowed/divorced/separated, and never married. Smoking status was classified into ever smokers (those who had smoked more than 100 cigarettes, including both former and

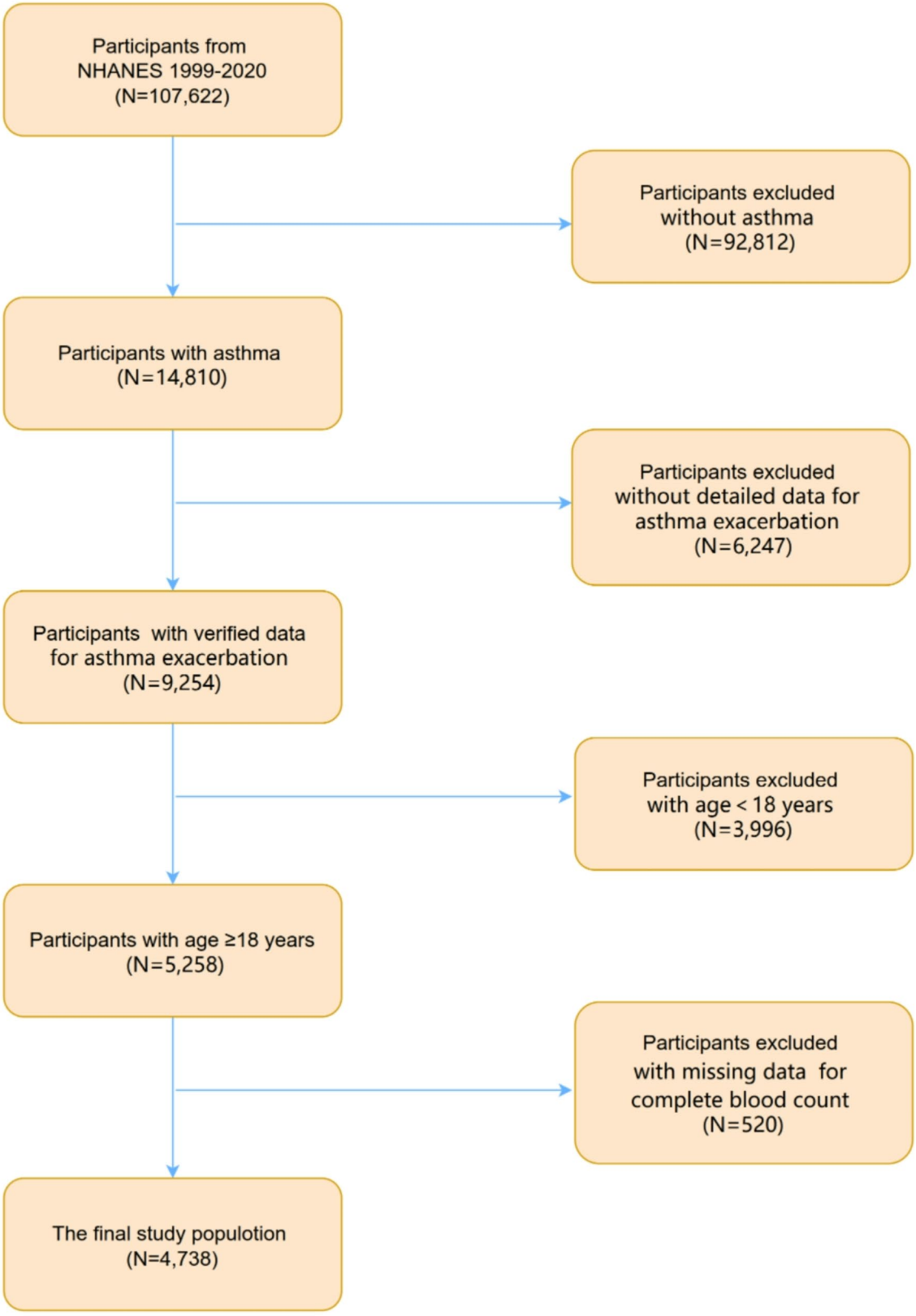

Fig. 1 Flowchart of participant selection and exclusion. Abbreviation: NHANES, National Health and Nutrition Examination Survey

current smokers) and never smokers (those who had smoked fewer than 100 cigarettes in their lifetime). Glucocorticoid usage was obtained from the prescription medication section of the sample person questionnaire, which collects data on the use of prescription medications in the month prior to the survey. This included inhaled glucocorticoids such as budesonide, fluticasone, and mometasone, as well as systemic glucocorticoids, including prednisolone, methylprednisolone, hydrocortisone, dexamethasone, and prednisone. CORD was defined as self-reported diagnoses of chronic obstructive pulmonary disease (COPD), chronic bronchitis, or emphysema. Similarly, hypertension, diabetes, CHF, CHD, and malignancy were based on self-reported diagnoses. More detailed information on these variables can be found on the NHANES website [11].

Statistical analyses

NHANES sample weights (WTMEC2YR or WTMEC4YR) were applied following NHANES protocols [18]. For combined data from the NHANES 1999–2000 and 2001–2002 cycles, four-year weights (WTMEC4YR) were used, while two-year weights (WTMEC2YR) were applied to data from 2003 to 2020. Sampling weights across the 1999–2020 cycles were calculated as follows: 4/23.2 × WTMEC4YR for 1999–2002, 3.2/23.2 × WTMEC2YR for the pre-pandemic period (2017–March 2020). Further details can be found in the NHANES Survey Methods and Analytic Guidelines.

Weighted analyses were conducted to ensure representativeness of the general population. Covariates with ≤ 20% missing data were handled using multiple imputation, while those with > 20% missing data were excluded to maintain accuracy and reliability in the estimates (Supplementary Materials, Table S1). Outliers were addressed using winsorization, with the 5th and 95th percentiles set as cutoff thresholds. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test, confirming that all continuous variables were non-normally distributed. As a result, continuous variables are reported as medians with interquartile ranges (IQRs), while categorical variables are presented as frequencies and percentages. Differences in asthma participant characteristics by asthma status were examined using the Wilcoxon rank-sum test for continuous variables and chi-square tests for categorical variables. Additionally, participants were stratified by EMR quartiles, with p-values obtained from analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables.

Logistic regression was applied to examine the association between EMR and asthma exacerbations, reporting odds ratios (OR) with 95% confidence intervals (CI). Linear trends across EMR levels and asthma exacerbations were evaluated using a trend test, treating EMR both as a continuous variable and as a categorical variable based on quartiles, with the quartile categories treated as a continuous variable. Three models were constructed: Model 1 was unadjusted; Model 2 adjusted for age, gender, race, and marital status; and Model 3 further adjusted for BMI, WBC count, neutrophil count, lymphocyte count, smoking status, glucocorticoid usage, CORD, hypertension, diabetes, CHF, CHD, and malignancy.

Subgroup analyses were performed to evaluate subgroup heterogeneity and interactions. Stratified analyses were conducted based on age (< 60 vs. ≥60 years), gender, race (Non-Hispanic White vs. others), marital status (married/partnered vs. others), smoking status (ever-smokers vs. never-smokers), BMI (< 25 vs. ≥25 kg/m^2), and the presence of comorbidities, including CORD, hypertension, diabetes, chronic heart failure, coronary heart disease, and malignancy. Restricted cubic spline (RCS) analysis was employed to explore potential nonlinear relationships and to identify threshold effects in the association between EMR and asthma exacerbations.

Sensitivity analyses were conducted throughout the study to enhance the robustness of the findings. First, EMR was assessed both as a continuous variable and by quartiles (using categorical and continuous formats). Second, the association was examined across models with progressive adjustments (Model 1, Model 2, and Model 3). Third, subgroup analyses were performed by stratifying participants based on age, gender, BMI, and comorbidities. Finally, the analyses were repeated after excluding participants with missing data in covariates. These approaches collectively ensured consistency and validated the results.

All data analyses were conducted using R software (version 4.4.2; R Foundation for Statistical Computing) with the R survey package (version 4.1.1) and Decisionlinnc software (version 1.1.1; Statsape Co., Ltd). A two-sided p-value < 0.05 was considered statistically significant.

Results

Patient baseline and clinical characteristics

Table 1 shows significant associations between asthma exacerbation and various demographic and clinical factors. Exacerbation was associated with female gender (68.63% vs. 60.14%, $p < 0.001$), Non-Hispanic White race (70.23% vs. 70.67%, $p = 0.039$), and higher BMI (29.93 [25.10–35.64] vs. 28.28 [24.22–33.73] kg/m^2, $p < 0.001$). Similar associations were observed with higher levels of WBC (7.50 [6.10–9.00] vs. 7.20 [6.00–8.80] × 10^3/μL, $p = 0.010$), lymphocytes (2.10 [1.70–2.60] vs. 2.00 [1.60–2.50] × 10^3/μL, $p < 0.001$), eosinophils (0.20 [0.10–0.30] vs. 0.20 [0.10–0.30] × 10^3/μL, $p = 0.003$), and EMR (0.40 [0.25–0.60] vs. 0.33 [0.20–0.50], $p < 0.001$). Additionally, exacerbation was linked to a higher prevalence

Table 1 Demographic and clinical characteristics of NHANES participants grouped by asthma status

	Overall, weighted *N* = 16,808,474	**Control group, weighted *N* = 8,951,244**	**Exacerbation group, weighted *N* = 7,857,230**	***p***
Age, years	45.00 (31.00–59.00)	45.00 (30.00–61.00)	45.00 (31.00–57.00)	0.309
Gender				< 0.001
Male	6,033,423 (35.90)	3,568,266 (39.86)	2,465,157 (31.37)	
Female	10,775,051 (64.10)	5,382,978 (60.14)	5,392,073 (68.63)	
Race				0.039
Mexican American	766,575 (4.56)	441,965 (4.94)	324,609 (4.13)	
Other Hispanic	999,962 (5.95)	511,858 (5.72)	488,104 (6.21)	
Non-Hispanic White	11,844,179 (70.47)	6,326,231 (70.67)	5,517,948 (70.23)	
Non-Hispanic Black	2,143,451 (12.75)	1,188,723 (13.28)	954,729 (12.15)	
Other	1,054,308 (6.27)	482,467 (5.39)	571,840 (7.28)	
Marital status				0.474
Married/Living with partner	9,348,961 (55.62)	5,050,729 (56.42)	4,298,231 (54.70)	
Widowed/Divorced/Separated	4,072,345 (24.23)	2,081,880 (23.26)	1,990,465 (25.33)	
Never	3,387,168 (20.15)	1,818,634 (20.32)	1,568,534 (19.96)	
BMI, kg/m^2	29.00 (24.43–34.70)	28.28 (24.22–33.73)	29.93 (25.10–35.64)	< 0.001
WBC, $10^3/\mu L$	7.30 (6.00–8.90)	7.20 (6.00–8.80)	7.50 (6.10–9.00)	0.010
Neutrophils, $10^3/\mu L$	4.30 (3.40–5.50)	4.20 (3.40–5.40)	4.30 (3.40–5.60)	0.269
Lymphocytes, $10^3/\mu L$	2.10 (1.70–2.50)	2.00 (1.60–2.50)	2.10 (1.70–2.60)	< 0.001
Monocytes, $10^3/\mu L$	0.60 (0.40–0.70)	0.60 (0.40–0.70)	0.50 (0.40–0.70)	0.125
Eosinophils, $10^3/\mu L$	0.20 (0.10–0.30)	0.20 (0.10–0.30)	0.20 (0.10–0.30)	0.003
EMR	0.33 (0.20–0.57)	0.33 (0.20–0.50)	0.40 (0.25–0.60)	< 0.001
Glucocorticoid usage				< 0.001
No	13,642,977 (81.17)	7,695,978 (85.98)	5,946,999 (75.69)	
Inhaled	2,645,411 (15.74)	1,105,331 (12.35)	1,540,080 (19.60)	
Systemic	520,086 (3.09)	149,935 (1.68)	370,151 (4.71)	
Smoking status				0.230
Ever	8,386,142 (49.89)	4,380,668 (48.94)	4,005,474 (50.98)	
Never	8,422,332 (50.11)	4,570,576 (51.06)	3,851,756 (49.02)	
CORD				< 0.001
No	12,148,077 (72.27)	6,903,088 (77.12)	5,244,990 (66.75)	
Yes	4,660,397 (27.73)	2,048,156 (22.88)	2,612,240 (33.25)	
Hypertension				0.778
No	10,596,048 (63.04)	5,663,676 (63.27)	4,932,372 (62.77)	
Yes	6,212,426 (36.96)	3,287,568 (36.73)	2,924,858 (37.23)	
Diabetes				0.647
No	14,777,976 (87.92)	7,889,974 (88.14)	6,888,002 (87.66)	
Yes	2,030,498 (12.08)	1,061,270 (11.86)	969,228 (12.34)	
CHF				0.025
No	15,920,318 (94.72)	8,542,697 (95.44)	7,377,621 (93.90)	
Yes	888,156 (5.28)	408,547 (4.56)	479,609 (6.10)	
CHD				0.173
No	15,983,332 (95.09)	8,555,599 (95.58)	7,427,733 (94.53)	
Yes	825,142 (4.91)	395,645 (4.42)	429,497 (5.47)	
Malignancy				0.610
No	14,829,834 (88.23)	7,926,778 (88.56)	6,903,056 (87.86)	
Yes	1,978,640 (11.77)	1,024,466 (11.44)	954,174 (12.14)	

Weighted analyses were performed to represent the general population. Continuous variables are expressed as median (interquartile range), and *p*-values are calculated using weighted t-tests. Categorical variables are presented as frequencies (percentages), with *p*-values determined using weighted chi-square tests

Abbreviations: BMI, body mass index; WBC, white blood cell count; EMR, eosinophil-to-monocyte ratio; CORD, chronic obstructive respiratory diseases; CHF, chronic heart failure; CHD, coronary heart disease

of comorbidities, including CORD (33.25% vs. 22.88%, $p < 0.001$) and CHF (6.10% vs. 4.56%, $p = 0.010$).

The results presented in Table 2 show associations between characteristics and EMR quartiles. Both age and BMI were positively associated with increasing EMR quartiles ($p = 0.019$ and $p = 0.003$, respectively), while eosinophil counts exhibited a progressive increase across quartiles ($p < 0.001$). In contrast, WBC, neutrophils, and monocytes were negatively associated with increasing EMR quartiles ($p = 0.424$, $p = 0.002$, and $p < 0.001$, respectively). Asthma exacerbation was significantly associated with EMR quartiles, with exacerbation rates increasing as EMR values rose, from 46.38% in the fourth quartile to 57.12% in the first quartile ($p < 0.001$). No significant associations were found for other clinical variables, including CORD, hypertension, diabetes, CHF, and CHD, across quartiles.

Association between the EMR and asthma exacerbation

The results in Table 3 present the association between EMR and asthma exacerbation as assessed through logistic regression across three models. When analyzed as a continuous variable, EMR was significantly associated with asthma exacerbation in all models ($p < 0.001$). When analyzed by quartiles as a categorical variable, in Model 1, the odds ratio (OR) for asthma exacerbation in Q4 (> 0.57) compared to the reference group Q1 (< 0.20) was 1.54 (95% CI: 1.23, 1.93, $p < 0.001$). Following adjustments in Model 2 and Model 3, the OR for Q4 vs. Q1 increased to 1.56 (95% CI: 1.24, 1.97, $p < 0.001$) and 1.58 (95% CI: 1.24, 2.02, $p < 0.001$), respectively. Additionally, the trend test indicated a significant positive association across quartiles as a continuous variable in all models ($p < 0.001$).

Subgroup analysis and non-linear curve fitting

Figure 2 presents the results of the subgroup analysis and interaction tests for the association between EMR and asthma exacerbation, adjusted for covariates in Model 3. No significant interactions were observed between EMR and any subgroup variables (all p for interaction > 0.05). The odds ratio (OR) for females was 1.67 (95% CI: 1.26, 2.22, $p < 0.001$), and for males, it was 1.50 (95% CI: 0.99, 2.27, $p = 0.059$), but the p for interaction for gender was 0.733, indicating no significant difference in the EMR–exacerbation relationship between genders. For age, the OR for participants aged < 60 was 1.70 (95% CI: 1.27, 2.29, $p = 0.001$), compared to 1.43 (95% CI: 0.96, 2.12, $p = 0.082$) for those aged ≥ 60, with a p for interaction of 0.226, suggesting no significant difference in the relationship by age. Similarly, no significant interactions were observed for race, BMI, marital status, smoking status, or comorbidities (CHF, CHD, diabetes, hypertension, and CORD), as all p-values for interaction were > 0.05.

Additionally, the RCS analysis was conducted to assess the relationship between continuous EMR levels and asthma exacerbation risk in Model 3, adjusting for potential confounders. No evidence of a non-linear relationship was observed ($p = 0.117$), as shown in Fig. 3. The smooth curve indicates a consistent increase in the odds ratio, suggesting a linear relationship between EMR and exacerbation risk within the observed range.

Sensitivity analysis

Sensitivity analyses remained consistent throughout the study process. EMR was examined as both a continuous variable and a quartile-based categorical variable, as well as analyzed within quartiles as a continuous measure. The relationship between EMR and exacerbation was evaluated through different adjustment strategies, including unadjusted, demographic-adjusted, and fully adjusted models. Subgroup analyses were carried out by stratifying key covariates to identify potential variations. After excluding participants with missing covariate data, repeated analyses yielded results consistent with those obtained after multiple imputation of covariates (see Supplementary Materials: Tables S2 and Fig. S1–S2). These comprehensive assessments reinforce the robustness and reliability of the conclusions.

Discussion

One of the most critical aspects of asthma pathophysiology is the recruitment of eosinophils to the airways during exacerbations. Eosinophils release cytotoxic proteins that damage the epithelium and perpetuate airway inflammation, strongly linking eosinophil-driven inflammation to more severe asthma and an increased risk of exacerbation [19]. In addition to eosinophils, neutrophils are also implicated in asthma, particularly in severe and corticosteroid-resistant phenotypes [20]. Monocytes, which can differentiate into macrophages and dendritic cells, also play a pivotal role in orchestrating immune responses and promoting airway remodeling, particularly in the context of chronic inflammation. These processes contribute to persistent immune dysregulation and may lead to the airway remodeling associated with more severe asthma phenotypes [21–23].

In this study, Table 1 revealed significant differences in WBC counts, lymphocyte counts, and eosinophil counts between the asthma exacerbation group and the control group, suggesting that systemic inflammation plays a crucial role in asthma exacerbations. Eosinophils, by releasing cytotoxic proteins and inflammatory mediators, contribute to epithelial damage and sustained airway inflammation, a mechanism particularly prominent in eosinophilic asthma phenotypes [2]. Elevated WBC counts and lymphocyte counts ($p = 0.010$ and $p < 0.001$, respectively) further reflect the activation of systemic

Table 2 Demographic and clinical characteristics of NHANES participants grouped by EMR quartiles

	Q1 (<0.20), weighted *N* = 4,205,891	Q2 (0.20–0.33), weighted *N* = 4,204,679	Q3 (0.33–0.50), weighted *N* = 4,310,626	Q4 (>0.50), weighted *N* = 4,085,700	*p*
Age, years	43.00 (28.00–59.00)	44.00 (31.00–59.00)	45.00 (34.00–59.00)	45.00 (31.00–59.00)	0.019
Gender					0.018
Male	1,355,923 (32.24%)	1,496,477 (35.59%)	1,533,754 (35.58%)	1,647,269 (40.32%)	
Female	2,849,968 (67.76%)	2,708,202 (64.41%)	2,776,872 (64.42%)	2,438,431 (59.68%)	
Race					0.017
Mexican American	185,961 (4.42%)	168,023 (4.00%)	222,302 (5.16%)	190,288 (4.66%)	
Other Hispanic	224,681 (5.34%)	191,966 (4.57%)	253,964 (5.89%)	329,351 (8.06%)	
Non-Hispanic White	2,915,058 (69.31%)	3,048,592 (72.50%)	3,083,869 (71.54%)	2,795,081 (68.41%)	
Non-Hispanic Black	616,215 (14.65%)	481,619 (11.45%)	511,122 (11.86%)	534,496 (13.08%)	
Other	263,976 (6.28%)	314,479 (7.48%)	239,370 (5.55%)	236,483 (5.79%)	
Marital status					0.516
Married/Living with partner	2,227,696 (52.97%)	2,349,580 (55.88%)	2,425,487 (56.27%)	2,344,619 (57.39%)	
Widowed/Divorced/Separated	1,024,659 (24.36%)	1,024,348 (24.36%)	1,085,610 (25.18%)	937,728 (22.95%)	
Never	953,535 (22.67%)	830,751 (19.76%)	799,529 (18.55%)	803,353 (19.66%)	
BMI, kg/m^2	28.08 (23.90–33.70)	28.80 (24.39–35.00)	29.81 (25.10–35.02)	29.39 (25.10–34.99)	0.003
WBC, 10^3/μL	7.40 (6.20–8.90)	7.30 (5.90–8.90)	7.30 (5.90–8.90)	7.30 (6.10–8.80)	0.424
Neutrophils, 10^3/μL	4.50 (3.50–5.70)	4.40 (3.40–5.50)	4.20 (3.30–5.60)	4.10 (3.40–5.20)	0.002
Lymphocytes, 10^3/μL	2.10 (1.70–2.50)	2.00 (1.60–2.50)	2.00 (1.70–2.60)	2.10 (1.70–2.60)	0.525
Monocytes, 10^3/μL	0.60 (0.50–0.70)	0.60 (0.40–0.70)	0.50 (0.40–0.70)	0.50 (0.40–0.60)	< 0.001
Eosinophils, 10^3/μL	0.10 (0.10–0.10)	0.20 (0.10–0.20)	0.20 (0.20–0.30)	0.40 (0.30–0.60)	< 0.001
Glucocorticoid usage					0.296
No	3,462,051 (82.31%)	3,442,841 (81.88%)	3,543,170 (82.20%)	3,193,337 (78.16%)	
Inhaled	597,808 (14.21%)	641,228 (15.25%)	650,386 (15.09%)	755,989 (18.50%)	
Systemic	146,032 (3.47%)	120,610 (2.87%)	117,070 (2.72%)	136,374 (3.34%)	
Asthma status					< 0.001
Exacerbation	2,402,487 (57.12%)	2,346,396 (55.80%)	2,305,977 (53.50%)	1,894,805 (46.38%)	
Control	1,803,403 (42.88%)	1,858,283 (44.20%)	2,004,649 (46.50%)	2,190,895 (53.62%)	
Smoking status					0.258
Ever	2,034,125 (48.36%)	2,089,003 (49.68%)	2,278,962 (52.87%)	1,982,472 (48.52%)	
Never	2,171,765 (51.64%)	2,115,676 (50.32%)	2,031,663 (47.13%)	2,103,228 (51.48%)	
CORD					0.242
No	3,044,978 (72.40%)	2,949,674 (70.15%)	3,085,167 (71.57%)	3,066,680 (75.06%)	
Yes	1,160,912 (27.60%)	1,255,005 (29.85%)	1,225,459 (28.43%)	1,019,020 (24.94%)	
Hypertension					0.390
No	2,723,721 (64.76%)	2,560,721 (60.90%)	2,684,467 (62.28%)	2,625,560 (64.26%)	
Yes	1,482,170 (35.24%)	1,643,958 (39.10%)	1,626,158 (37.72%)	1,460,140 (35.74%)	
Diabetes					0.266
No	3,777,168 (89.81%)	3,650,600 (86.82%)	3,786,169 (87.83%)	3,562,460 (87.19%)	
Yes	428,723 (10.19%)	554,079 (13.18%)	524,457 (12.17%)	523,240 (12.81%)	
CHF					0.571
No	3,998,139 (95.06%)	3,946,386 (93.86%)	4,077,078 (94.58%)	3,897,136 (95.38%)	
Yes	207,752 (4.94%)	258,293 (6.14%)	233,547 (5.42%)	188,564 (4.62%)	
CHD					0.719
No	4,016,549 (95.50%)	3,969,728 (94.41%)	4,093,514 (94.96%)	3,901,963 (95.50%)	
Yes	189,342 (4.50%)	234,951 (5.59%)	217,112 (5.04%)	183,737 (4.50%)	
Malignancy					0.697
No	3,719,721 (88.44%)	3,667,674 (87.23%)	3,787,737 (87.87%)	3,653,123 (89.41%)	
Yes	486,170 (11.56%)	537,005 (12.77%)	522,889 (12.13%)	432,577 (10.59%)	

Weighted analyses were performed to represent the general population. Continuous variables are expressed as median (interquartile range), and *p*-values are calculated using weighted t-tests. Categorical variables are presented as frequencies (percentages), with *p*-values determined using weighted chi-square tests

Abbreviations: Q1–4, quartile 1–4; BMI, body mass index; WBC, white blood cell count; EMR, eosinophil-to-monocyte ratio; CORD, chronic obstructive respiratory diseases; CHF, chronic heart failure; CHD, coronary heart disease

Table 3 Association between EMR and asthma exacerbation across multiple models

	Model 1		Model 2		Model 3	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
EMR (continuous)		<0.001		<0.001		<0.001
EMR (quartile)						
Q1	reference		reference		reference	
Q2	1.06 (0.86, 1.29)	0.605	1.04 (0.85, 1.27)	0.708	1.03 (0.84, 1.27)	0.743
Q3	1.16 (0.93, 1.44)	0.180	1.14 (0.92, 1.42)	0.228	1.16 (0.93, 1.46)	0.184
Q4	1.54 (1.23, 1.93)	<0.001	1.56 (1.24, 1.97)	<0.001	1.58 (1.24, 2.02)	<0.001
p for trend	<0.001		<0.001		<0.001	

Model 1: unadjusted

Model 2: adjusted for age, gender, race and marital status

Model 3: further adjusted for BMI, WBC, neutrophils, lymphocyte, glucocorticoid usage, smoking status, CORD, hypertension, diabetes, CHF, CHD, and malignancy

Abbreviations: OR, odds ratio; CI, confidence interval; EMR, eosinophil-to-monocyte ratio; Q1–Q4, quartiles 1–4; BMI, body mass index; WBC, white blood cell count, CORD, chronic obstructive respiratory diseases; CHF, chronic heart failure; CHD, coronary heart disease

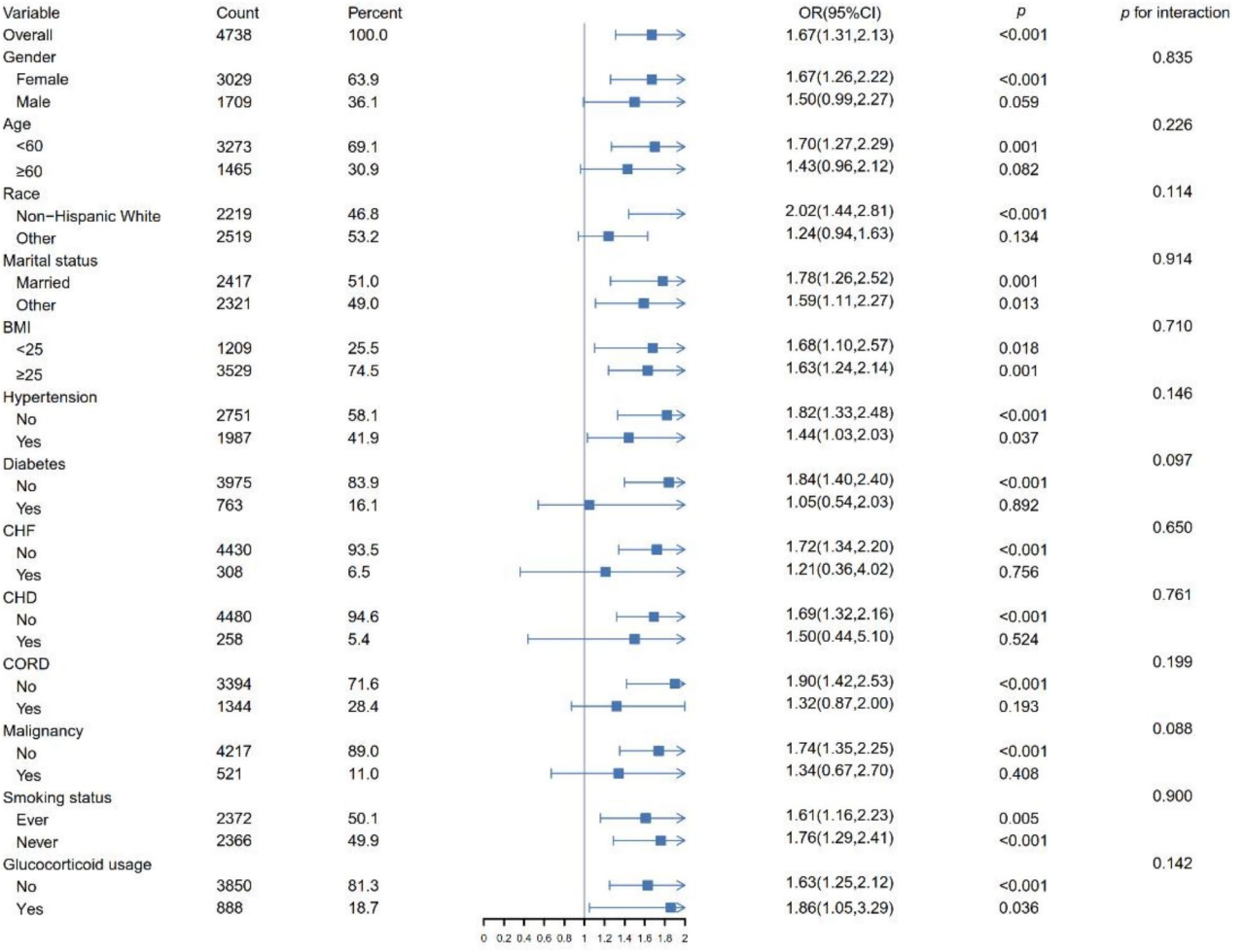

Fig. 2 Subgroup analysis of the association between EMR and asthma exacerbation. Abbreviations: EMR, eosinophil-to-monocyte ratio; OR, odds ratio; BMI, body mass index; CHF, chronic heart failure; CHD, coronary heart disease; CORD, chronic obstructive respiratory diseases

inflammatory responses during acute asthma exacerbations. While WBC counts serve as a nonspecific marker potentially indicative of both acute inflammation and underlying infections [24], lymphocytes are likely involved in adaptive immune regulation of airway inflammation [25].

In our preliminary analysis, the independent predictive value of these single inflammatory markers was

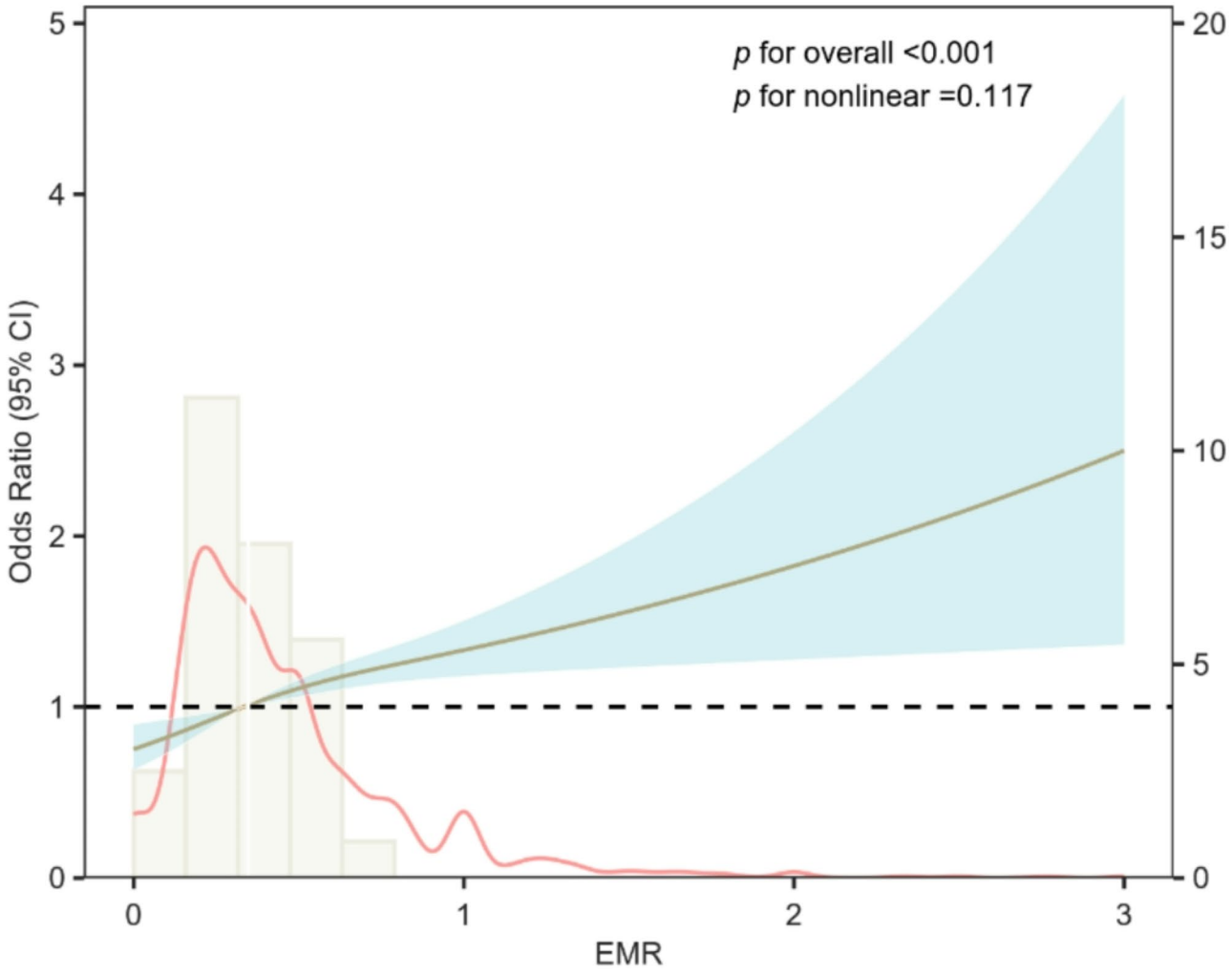

Fig. 3 Restricted cubic spline analysis of EMR and asthma exacerbation risk in Model 3. Abbreviations: CI, confidence interval; EMR, eosinophil monocyte ratio

further examined. Although univariate logistic regression analyses showed significant associations between WBC, lymphocyte counts, eosinophil counts, and acute exacerbations. Trend tests in multivariable-adjusted models (Model 2 and Model 3) revealed no significant associations for these markers. Similarly, monocyte counts did not demonstrate statistical significance across any of the models. These findings highlight the limitations of using single-cell counts to predict asthma exacerbations and underscore the necessity for more integrative biomarkers. While eosinophil counts are widely used as biomarkers in asthma, especially in guiding the administration of corticosteroids and biologics therapies [26], the inclusion of monocytes in the EMR provides an additional layer of insight. By combining the allergic inflammatory effects of eosinophils with the chronic inflammatory contributions of monocytes, EMR offers a comprehensive tool for assessing systemic inflammation levels. Our results indicate that trend tests for EMR in all models consistently demonstrated significant associations ($p < 0.001$), underscoring its reliability and superiority in predicting asthma exacerbations. These findings further reinforce the potential of EMR as a more sensitive and holistic biomarker compared to single-cell counts.

BMI was significantly higher in the exacerbation group compared to the control group (29.93 [25.10–35.64] vs. 28.28 [24.22–33.73] kg/m², $p < 0.001$) in Table 1, consistent with the well-established link between obesity and asthma. Obesity not only increases airway resistance through mechanical effects but also exacerbates asthma symptoms by influencing systemic inflammation, adipokine secretion, and metabolic dysregulation [27–28]. The inflammatory characteristics associated with obesity may involve non-eosinophilic mechanisms, further contributing to airway remodeling and reduced responsiveness to therapy.

Additionally, Table 1 shows that the prevalence of CORD (including COPD, chronic bronchitis, and

emphysema) was significantly higher in the exacerbation group compared to the control group (33.25% vs. 22.88%, $p < 0.001$). Previous studies have demonstrated that patients with asthma-COPD overlap syndrome (ACOS) typically exhibit a greater inflammatory burden and a higher risk of acute exacerbations [29–30]. Pathological features of COPD, such as airway remodeling and chronic bronchitis, may act synergistically with asthma exacerbations, further aggravating airway obstruction and inflammatory load [31]. Therefore, the significant increase in CORD prevalence may reflect elevated levels of both systemic and localized inflammation in the exacerbation group.

Given that our subgroup analyses did not reveal any significant interaction effects, it suggests that EMR's predictive value is not influenced by demographic factors such as age, gender, or comorbidities. This highlights the potential of EMR as a universal marker across a broad patient population, independent of these confounding variables. Such a finding is valuable, as it suggests that EMR could be used universally across different populations to predict exacerbation risk, further enhancing its clinical utility.

The lack of a non-linear relationship between EMR and asthma exacerbation risk, as demonstrated by restricted cubic spline analysis, indicates that the association remains linear across a wide range of EMR levels. This finding simplifies the clinical interpretation of EMR as a continuous variable. Unlike other markers that may have threshold effects [32], EMR appears to show a proportional increase in exacerbation risk as levels rise, making it easier to apply in routine practice for risk stratification.

Limitations of this study include its cross-sectional design, which limits our ability to draw causal inferences. Longitudinal studies are necessary to determine whether elevated EMR levels precede exacerbations or merely reflect an ongoing inflammatory state. Furthermore, the use of self-reported data for asthma exacerbations could introduce recall bias, though this has been minimized by using validated measures. Additionally, this study did not differentiate between asthma phenotypes, such as eosinophilic and non-eosinophilic asthma [33–34], which could influence the generalizability of our findings.

Future research should focus on validating the use of EMR in prospective cohort studies and exploring the potential mechanisms linking EMR to asthma exacerbations. Such studies could investigate whether interventions targeting both eosinophilic and monocytic inflammation could effectively reduce EMR levels and thereby mitigate exacerbation risk. Additionally, it would be valuable to explore whether EMR could be used in combination with other biomarkers, such as fractional exhaled nitric oxide (FeNO) or serum periostin [35–36], to improve the overall prediction and management of asthma exacerbations.

Conclusion

This study suggests that EMR is a valuable biomarker for predicting asthma exacerbations, independent of traditional risk factors. Its linear relationship with exacerbation risk and applicability across diverse populations make it a promising tool for personalized asthma management.

Abbreviations

NHANES	National Health and Nutrition Examination Survey
EMR	Eosinophil-to-monocyte ratio
PE	Pulmonary embolism
CAP	Community-acquired pneumonia
STEMI	ST-elevation myocardial infarction
AIS	Acute ischemic stroke
STROBE	Strengthening the reporting of observational studies in epidemiology
IRB	the Institutional Review Board
NCHS	the National Center for Health Statistics
CBC	Complete blood count
MEC	Mobile Examination Center
WBC	White blood cell count
BMI	Body mass index
CORD	Chronic obstructive respiratory disease
COPD	Chronic obstructive pulmonary disease
IQRs	Interquartile ranges (IQRs)
CHF	Chronic heart failure
CHD	Coronary heart disease
SD	Standard deviation
ANOVA	Analysis of variance
OR	Odds ratio
CI	Confidence interval
RCS	Restricted cubic spline
ACOS	Asthma-COPD overlap syndrome
FeNO	Fractional exhaled nitric oxide

Supplementary Information

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Supplementary Material 1

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Author contributions

Congyi Xie was responsible for conceptualization, data curation, methodology development, and drafting the original manuscript. Jinzhan Chen contributed to investigation, data curation, formal analysis, and critically reviewed and edited the manuscript. Haiyan Chen provided supporting contributions to investigation, data curation, visualization, and manuscript review and editing. Ning Zhang oversaw the study's conceptualization, supervision, and project administration, contributed to manuscript review and editing, secured funding, and served as the corresponding author.

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Data availability
The datasets utilized in this study are publicly accessible through established repositories. Supporting data for this research can be found on the NHANES website (https://wwwn.cdc.gov/Nchs/Nhanes/).

Declarations

Ethics approval and consent to participate
NHANES protocols and consent procedures were approved by the NCHS Research Ethics Review Board. Written informed consent was obtained from all participants, and the study adhered to STROBE guidelines to maintain rigorous methodological and ethical standards. For further details, please refer to NCHS NHANES and NCHS ERB Approval.

Consent for publication
No individual personal information is disclosed in this publication, and all data have been de-identified to maintain participant confidentiality.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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