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Elevated inflammatory burden index increases mortality in adults with chronic inflammatory airway diseases: a nationwide cohort study

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Abstract

Objective The objective of this study was to investigate the potential association between the inflammatory burden index (IBI) and the prevalence of chronic inflammatory airway diseases (CIAD), as well as mortality rates among individuals diagnosed with CIAD.

Methods Participants were sourced from the National Health and Nutrition Examination Survey (NHANES) conducted between 1999 and 2010. The IBI was calculated using the formula: IBI = C-reactive protein * neutrophils / lymphocytes. CIAD comprised self-reported asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD). Mortality outcomes, including all-cause and respiratory disease mortality, were determined through linked data from the National Death Index (NDI) up to December 2019.

Results A total of 27,495 adults were included. IBI was divided into quartiles, with the lowest quartile as the reference group. After adjusting for confounding variables, a positive correlation was observed between higher IBI and increased prevalence of total CIAD (OR = 1.383 [1.215–1.575]), asthma (OR = 1.267 [1.096–1.465]), chronic bronchitis (OR = 1.568 [1.263–1.946]), and COPD (OR = 1.907 [1.311–2.774]). Over a median follow-up of 12.33 [9.92-16.00] years, there were 1221 deaths from all causes and 220 deaths from respiratory disease among 4499 patients with CIAD. Following multivariate adjustments, the fourth quartile was significantly associated with increased risk of all-cause mortality (HR = 2.227 [1.714–2.893]) and respiratory disease mortality (HR = 2.748 [1.383–5.459]) compared to the first quartile of IBI in CIAD participants. Moreover, variable importance analysis using a random survival forest model demonstrated the significance of IBI in predicting mortality from both all-cause and respiratory diseases.

Conclusion IBI exhibited an association with the prevalence of CIAD, with higher IBI levels correlating with elevated all-cause and respiratory disease mortality among individuals with CIAD.

Keywords IBI, CIAD, Asthma, Chronic bronchitis, COPD, Mortality, NHANES

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Introduction

Chronic inflammatory airway diseases (CIAD), including asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD), have garnered significant public health attention [1, 2]. Factors such as industrialization, an aging population, and urbanization have led to a gradual increase in the prevalence and mortality rates of various chronic respiratory diseases [3]. The primary attributions to this trend include factors such as air pollution, tobacco exposure, and unhealthy lifestyles [4, 5]. In 2017, chronic respiratory diseases ranked as the third leading cause of mortality globally, following cardiovascular diseases and cancer, accounting for 7.0% of all deaths [2]. Among chronic respiratory diseases, asthma and COPD emerged as the most prevalent conditions [6–8]. The high prevalence and morbidity of these diseases lead to a significant financial burden on the healthcare system [9–11].

The pathogenesis of CIAD is intricate and influenced by a variety of environmental and genetic factors [12, 13]. Systemic inflammation and immune response may have a significant impact on the progression of chronic airway inflammation, serving as a pivotal pathogenic mechanism [14, 15]. Numerous inflammatory cells are recruited to and activated in the airways, contributing to the inflammatory and immune response [12]. Each of these cells releases various mediators that subsequently exert effects on the airway. Elevated levels of inflammatory markers, including C-reactive protein (CRP), neutrophil counts, and lymphocyte counts, have been shown to correlate with a heightened susceptibility to CIAD [16–19]. Razi et al. documented a rise in serum CRP levels during acute asthma, suggesting its potential utility as a diagnostic and monitoring tool for inflammation in such patients [20]. The meta-analysis conducted by Huang et al. demonstrated that the neutrophil-to-lymphocyte ratio (NLR) represents a viable and user-friendly indicator for asthma and its exacerbations [21]. Aksu et al. also observed an increase in CRP levels among stable COPD patients, regardless of smoking behavior and biomass exposure [22]. In patients with COPD, a systematic review and meta-analysis demonstrated a significant link between high baseline CRP levels and elevated mortality [19]. However, markers of inflammation and immune response, such as CRP, neutrophil counts, and lymphocyte counts, only offer partial insights into these processes. The relationship between a composite marker of inflammation and immune response and CIAD remains inadequately explored.

The inflammatory burden index (IBI) was a composite index that incorporates several inflammatory markers [23], including CRP, neutrophil counts and lymphocyte counts, to provide a more comprehensive assessment of systemic inflammation and immune response. The IBI was calculated using the formula: IBI = C-reactive protein * neutrophils / lymphocytes. Various studies had suggested that IBI offers more precise prognostic value for disease outcomes compared to individual markers. Pelc et al. noted that the IBI correlated with postoperative complications and mortality in gastric cancer patients receiving multimodal therapy [24]. The study by Xie et al. revealed that the IBI was independently linked to overall survival, hospitalization duration, expenses, and cachexia among patients with non-small cell lung cancer [25]. Song et al. found that a high IBI level was linked to poor functional outcomes in individuals with Aneurysmal Subarachnoid Hemorrhage [26]. He et al. found that an increase in the IBI was associated with higher all-cause mortality in the general population aged over 45 years. This association persisted even after adjusting for other confounding factors [27].

Several studies have investigated the correlation between mortality in patients with respiratory diseases and the NLR, indicating that systemic inflammation plays a pivotal role in various respiratory conditions [16–18]. These studies have demonstrated that an elevated NLR is associated with poorer prognoses in asthma and COPD patients. These findings suggest that the IBI, which integrates CRP, neutrophils, and lymphocytes, could be a relevant marker in these contexts. Despite these insights, the association between IBI and the prevalence and prognosis of respiratory diseases has not been thoroughly explored. The potential link between IBI and the prevalence of CIAD and mortality in CIAD patients remains uncertain. Understanding this relationship could yield valuable insights for clinical practice. To address this research gap, we analyzed data from the National Health and Nutrition Examination Survey (NHANES) spanning 1999 to 2010. Our study aimed to investigate the relationship between IBI and the prevalence of CIAD, encompassing asthma, chronic bronchitis, and COPD. Additionally, we examined how IBI influences overall mortality and mortality specifically related to respiratory diseases among individuals with CIAD. Our findings aim to provide scientific evidence and recommendations to enhance the prevention and management of respiratory illnesses.

Methods

Study population

Analysis was performed on data gathered from the National Health and Nutrition Examination Survey (NHANES) 1999–2010. NHANES, administered by the National Center for Health Statistics (NCHS), is a nationally representative survey of the US population [28, 29]. Utilizing a complex, multistage sampling design, the survey selected a representative sample of the US population. Participants over 20 years old with complete data

on relevant markers (CRP, neutrophils, and lymphocytes) and assessment of CIAD were included. Exclusions comprised pregnant individuals, those lacking CIAD assessment data, individuals with IBI, those under 20 years old, and those lacking follow-up information. The detailed flow chart can be found in Figure S1. In accordance with the guidelines of the National Center for Health Statistics Research Ethics Review Board (NCHS ERB), written informed consent was secured from all participants (refer to supplementary material), and the ensuing dataset has been made publicly accessible at https://www.cdc.gov/nchs/nhanes/.

Calculation of inflammatory burden index (IBI)

The IBI was computed for each participant by multiplying their CRP level by the ratio of their neutrophil count to lymphocyte count, represented as IBI=CRP * neutrophil/lymphocyte [23]. The Beckman Coulter MAXM instrument at the Mobile Examination Center (MEC) was utilized to conduct complete blood counts on blood samples and furnish a blood cell distribution for all participants. The derivation of complete blood count (CBC) parameters relies on the Beckman Coulter method for counting and sizing, coupled with an automated dilution and mixing apparatus for sample preparation, and a singular-beam photometer for hemoglobin measurement. The white blood cell count (WBC) differential employs VCS technology. CRP was quantified by latex-enhanced nephelometry. Higher IBI values signify a greater inflammatory burden. Participants were stratified into quartiles based on their IBI for analysis, with the first quartile denoting a low inflammatory burden and the fourth quartile indicating a high inflammatory burden (Quartile 1: <0.15; Quartile 2: 0.16–0.40; Quartile 3: 0.41–1.04; Quartile 4: >1.04).

Assessment of CIAD

Within this study, CIAD comprised self-reported asthma, chronic bronchitis, and COPD. Participants were asked about a prior diagnosis of asthma, chronic bronchitis, or COPD by a medical professional. Those who confirmed this were categorized as individuals with the respective condition. When asthma, chronic bronchitis, or COPD tests positive, it implies a positive diagnosis for CIAD. CIAD was defined as the presence of at least one self-reported case of asthma, chronic bronchitis, or COPD.

Assessment of all-cause and respiratory disease mortality

The study focused on all-cause and respiratory disease mortality, encompassing deaths from any cause and respiratory conditions. Mortality data were acquired by cross-referencing NHANES data with the National Death Index (https://www.cdc.gov/), using probabilistic matching based on personal identifiers such as name, date of birth, social security number, and sex. The duration of follow-up was determined from the NHANES interview date to the date of death or December 31, 2019, whichever occurred first. Respiratory disease mortality was classified as death caused by chronic lower respiratory diseases and influenza and pneumonia.

Covariates

In our analyses, we incorporated various covariates to account for potential confounders. These covariates, chosen from existing literature, encompassed factors such as age, sex, race, living situation, educational attainment, family poverty income ratio (PIR), smoking and alcohol consumption habits, BMI, physical activity levels, as well as Healthy Eating Index (HEI) and Charlson Comorbidity Index (CCI). Age was classified into three categories: 20–39 years, 40–59 years, and ≥60 years, and sex was categorized as female or male. Race/ethnicity was classified into Non-Hispanic White, Non-Hispanic Black, and other races. Living status was divided into two groups: alone or with partners, while education level was divided into three groups: below high school, high school, and above high school. Family poverty income ratio Income was assessed using the poverty income ratio (PIR, the ratio of family income divided by a poverty threshold specific for family size using guidelines from the US Department of Health and Human Services) and categorized as ≤1.0, 1.1-3.0 and >3.0. Smoking status was classified as never, former, or current smoker, while alcohol use was categorized as nondrinker, low-to-moderate drinker, or heavy drinker. Body mass index (BMI) was divided into three categories: <25.0, 25.0-29.9, and >29.9 kg/m^2. Physical activity levels were classified as inactive, insufficiently active, or active. Both the HEI-2015 score and CCI were treated as continuous variables. A detailed definition of potential confounding variables, such as family poverty income ratio, smoking status, drinking status, physical activity, HEI-2015, and CCI, was available in the supplementary material.

Statistical analysis

All statistical analyses we conduct were weighted in accordance with the NHANES analytic and reporting guidance. Normally distributed continuous variables were described as means and standard error (SE), while continuous variables without a normal distribution are presented as medians and interquartile ranges. Categorical variables were presented as numbers (percentages). To normalize their distributions, the IBI was log-transformed. The one-way ANOVA and the Chi-square test were used to determine the differences in means and distribution of general characteristics.

In this study, a multiple logistic regression model was employed to ascertain the adjusted odds ratios (ORs)

and 95% confidence intervals (CIs) for the association between quartiles of IBI and the prevalence of total and specific CIAD. To further explore the dose–response curves of this association, restricted cubic spline regression analysis was conducted with knots set at the 10th, 50th, and 90th percentiles of IBI. In prospective cohort studies, using the Kaplan–Meier method, cumulative survival rates were calculated and log-rank tests were used to compare the survival rates among four groups of participants, which were divided based on the quartiles of IBI. Additionally, multiple Cox regressions were implemented to calculate adjusted hazard ratios (HRs) and 95% CIs in relation to all-cause and respiratory disease mortality of participants with CIAD. Additionally, we used a Cox regression model with a restricted cubic spline to investigate the shape of the association between IBI and all-cause death and respiratory disease mortality, adjusting for the several covariates (including age, sex, and race/ethnicity, living status, education level, family PIR, BMI, drinking status, smoking status, physical activity, HEI, and CCI). To assess non-linearity, we utilized the likelihood ratio test. Furthermore, we also performed subgroup analysis to explore the relationship between IBI and all-cause and respiratory disease mortality in different subgroups. Time-dependent receiver-operator characteristic curve (ROC) analysis was conducted to evaluate the accuracy of IBI at different time points in predicting survival outcomes. We performed variable importance analysis using a random survival forest model to assess the importance of IBI and its components in predicting mortality among participants with CIAD.

To ensure robustness, we conducted four sensitivity analyses. Firstly, we performed COX regression on IBI quartiles for all-cause and respiratory mortality among asthma participants in NHANES 2001–2010. Secondly, we did a similar analysis for chronic bronchitis or COPD participants. Thirdly, we excluded participants who died within two years to address early mortality bias. Finally, we adjusted for respiratory agents, including selective phosphodiesterase-4 inhibitors, mast cell stabilizers, leukotriene modifiers, and inhaled corticosteroids, among CIAD participants. We performed all statistical analyses using R software (version 4.2.0). Statistical significance was defined as a two-tailed P value < 0.05.

Results

Characteristics of study participants

Between 1999 and 2010, a total of 62,160 participants were involved in the NHANES study, with 14,934 individuals lacking the necessary data to calculate IBI. Participants under 20 years old and those without CIAD assessment data ($n = 18,609$), as well as pregnant individuals ($n = 1,090$), were excluded. This resulted in 27,527 eligible participants for the analysis of IBI and CIAD risk. Furthermore, 32 participants who lacked follow-up data were excluded, leaving a final sample of 27,495 participants for subsequent analysis (Figure S1).

Table 1 presented the baseline characteristics of NHANES 1999–2010 participants categorized into quartiles based on their IBI. The study cohort predominantly comprised individuals under 60 years of age (76.91%), with a gender distribution of 51.06% female, and a predominant representation of non-Hispanic white individuals (71.45%). The prevalence rates of CIAD, asthma, chronic bronchitis, and COPD were 17.1%, 12.94%, 6.21%, and 1.76%, respectively. In comparison to the 6,876 participants in the first quartile of IBI, those with higher IBI were more likely to be older females of non-Hispanic white ethnicity, living alone, with lower education status, and a lower family PIR. They were also more likely to be current smokers, non-drinkers, have a higher BMI, engage in less physical activity, possess a lower HEI-2015 score, have a higher CCI, elevated levels of C-reactive protein, neutrophils, and lymphocytes, and exhibit a higher prevalence of CIAD, asthma, chronic bronchitis, and COPD. The baseline characteristics of participants, stratified by CIAD, were also presented in Table S1. In the context of survival analysis, 4,499 participants with CIAD and complete follow-up information were enrolled. The baseline characteristics of the participants, stratified by all-cause mortality, were further elucidated in Table S2.

Associations between IBI and the prevalence of CIAD among adults

In this study, IBI was classified into quartiles, with the lowest quartile as the reference category, and assessed for its association with the prevalence of total and specific CIAD (Table 2). The crude model revealed a positive correlation between IBI quartiles and the prevalence of both total and specific CIAD. After adjusting for age, sex, and race, this relationship remained statistically significant. Compared to the reference quartile, the third and fourth quartiles of IBI in Model 1 were associated with a higher prevalence of total CIAD, asthma, chronic bronchitis, and COPD. After correcting for more confounding factors, we found that the fourth quartile of IBI was significantly associated with a lower prevalence of total CIAD (OR = 1.383 [1.215–1.575]), asthma (OR = 1.267 [1.096–1.465]), chronic bronchitis (OR = 1.568 [1.263–1.946]), and COPD (OR = 1.907 [1.311–2.774]) compared to the lowest quartile in Model 2.

In addition, linear and positive associations were observed between IBI and the prevalence of CIAD (P for nonlinearity = 0.051, Figure S2A), asthma (P for nonlinearity = 0.134, Figure S2B), chronic bronchitis (P for nonlinearity = 0.756, Figure S2C), and COPD (P for nonlinearity = 0.291, Figure S2D). For

Table 1 Baseline characteristics of participants in adults according to quartiles of IBI in NHANES 1999–2010

Characteristics		Quartiles of IBI				*P* value
		< 0.15	0.16–0.40	0.41–1.04	> 1.04	
Participants	27,495	6876	66,882	6861	6876	
Age, %						< 0.001
20–39 years	8879(37.95)	3072(48.69)	2169(37.16)	1914(33.50)	1724(30.54)	
40–59 years	8870(38.96)	2155(36.39)	2306(39.98)	2199(40.03)	2210(39.82)	
≥ 60 years	9746(23.08)	1649(14.92)	2407(22.85)	2748(26.47)	2942(29.64)	
Sex, %						< 0.001
Female	13,745(51.06)	3026(46.01)	3123(45.55)	3593(53.45)	4003(60.80)	
Male	13,750(48.94)	3850(53.99)	3759(54.45)	3268(46.55)	2873(39.20)	
Race/ethnicity, %						< 0.001
Non-Hispanic White	13,715(71.45)	3338(70.06)	3422(71.52)	3465(72.39)	3490(72.04)	
Non-Hispanic Black	5261(10.52)	1471(11.18)	1207(9.63)	1232(9.77)	1351(11.50)	
Other race	8519(18.04)	2067(18.76)	2253(18.85)	2164(17.85)	2035(16.46)	
Living status, %						< 0.001
Alone	10,711(35.37)	2699(35.51)	2490(33.37)	2631(34.38)	2891(38.49)	
With partners	16,784(64.63)	4177(64.49)	4392(66.63)	4230(65.62)	3985(61.51)	
Education level, %						< 0.001
Below high school	8476(19.62)	1815(16.55)	2076(18.84)	2243(20.74)	2342(23.05)	
High school	6531(25.14)	1502(22.09)	1667(25.66)	1687(26.40)	1675(26.94)	
Above high school	12,488(55.23)	3559(61.36)	3139(55.50)	2931(52.86)	2859(50.01)	
Family PIR, %						< 0.001
≤ 1.0	5382(13.71)	1219(12.46)	1284(12.94)	1349(13.38)	1530(16.41)	
1.1–3.0	11,712(36.36)	2694(32.60)	2877(35.46)	3011(38.13)	3130(40.06)	
> 3.0	10,401(49.93)	2963(54.95)	2721(51.60)	2501(48.49)	2216(43.53)	
Smoking status, %						< 0.001
Never smoker	14,197(51.53)	3853(55.97)	3606(51.56)	3429(50.14)	3309(47.60)	
Former smoker	7136(24.72)	1567(22.92)	1798(25.02)	1881(25.35)	1890(25.88)	
Current smoker	6162(23.75)	1456(21.11)	1478(23.42)	1551(24.51)	1677(26.52)	
Drinking status, %						< 0.001
Nondrinker	6209(18.96)	1302(16.29)	1452(17.28)	1621(19.66)	1834(23.32)	
Low-to-moderate drinker	18,926(71.35)	4959(73.90)	4843(73.07)	4624(70.09)	4500(67.68)	
Heavy drinker	2360(9.69)	615(9.81)	587(9.65)	616(10.25)	542(9.00)	
Body mass index, %						< 0.001
< 25.0 kg/m^2	8178(32.59)	3471(54.11)	2046(32.01)	1464(23.00)	1197(17.28)	
25.0–29.9 kg/m^2	9641(34.07)	2427(33.08)	2827(40.51)	2467(34.82)	1920(27.27)	
> 29.9 kg/m^2	9676(33.35)	978(12.81)	2009(27.48)	2930(42.18)	3759(55.45)	
Physical activity, %						< 0.001
Inactive	7984(22.62)	1508(16.26)	1831(20.46)	2105(24.88)	2540(30.32)	
Insufficiently active	11,096(45.87)	2836(46.28)	2839(46.20)	2775(46.78)	2646(44.06)	
Active	8415(31.51)	2532(37.46)	2212(33.34)	1981(28.34)	1690(25.62)	
HEI-2015 score	49.40(40.40,58.82)	50.54(41.55,60.17)	50.01(40.91,59.43)	48.91(40.26,57.92)	47.61(38.95,57.12)	< 0.001
CCI	0.76(0.01)	0.52(0.01)	0.67(0.02)	0.82(0.02)	1.08(0.02)	< 0.001
C-reactive protein, mg/dL	0.19(0.07,0.43)	0.04(0.03,0.07)	0.14(0.10,0.18)	0.30(0.23,0.40)	0.85(0.57,1.36)	< 0.001
Neutrophil, 10^3/μL	4.10(3.20,5.10)	3.30(2.70,4.20)	3.90(3.10,4.80)	4.30(3.50,5.20)	5.10(4.10,6.30)	< 0.001
Lymphocyte, 10^3/μL	2.00(1.60,2.50)	2.00(1.70,2.50)	2.00(1.70,2.50)	2.00(1.60,2.50)	2.00(1.60,2.50)	< 0.001
CIAD, %						< 0.001
No	22,996(82.89)	5975(86.12)	5878(84.50)	5736(82.59)	5407(77.49)	
Yes	4499(17.11)	901(13.88)	1004(15.50)	1125(17.41)	1469(22.51)	
Asthma, %						< 0.001
No	24,176(87.06)	6159(88.78)	6118(87.96)	6051(87.07)	5848(83.98)	
Yes	3319(12.94)	717(11.22)	764(12.04)	810(12.93)	1028(16.02)	
Chronic bronchitis, %						< 0.001
No	25,859(93.79)	6617(96.07)	6549(94.86)	6434(93.40)	6259(90.24)	

Table 1 (continued)

Characteristics		Quartiles of IBI				*P* value
		< 0.15	0.16–0.40	0.41–1.04	> 1.04	
Yes	1636(6.21)	259(3.93)	333(5.14)	427(6.60)	617(9.76)	
COPD, %						< 0.001
No	26,903(98.24)	6809(99.15)	6768(98.71)	6720(98.14)	6606(96.72)	
Yes	592(1.76)	67(0.85)	114(1.29)	141(1.86)	270(3.28)	

Abbreviations IBI, inflammatory burden index; PIR, poverty income ratio; HEI-2015, Healthy Eating Index 2015; CCI, Charlson Comorbidity Index; CIAD, chronic inflammatory airway disease; COPD, chronic obstructive pulmonary disease. Normally distributed continuous variables are described as means ± SEs, and continuous variables without a normal distribution are presented as medians [interquartile ranges]. Categorical variables are presented as numbers (percentages). N reflect the study sample while percentages reflect the survey-weighted data

Table 2 Logistic regression analysis of quartiles of IBI levels with the prevalence of CIAD and its components among adults in NHANES 2001–2010 ($n = 27,495$)

	Quartiles of IBI levels				
	< 0.15	0.16–0.40	0.41–1.04	> 1.04	P_{trend}
CIAD					
Crude	1 (Ref)	1.138 (1.014–1.277)	1.308 (1.170–1.462)	1.803 (1.613–2.014)	< 0.001
Model 1	1 (Ref)	1.149 (1.021–1.293)	1.285 (1.146–1.441)	1.728 (1.540–1.939)	< 0.001
Model 2	1 (Ref)	1.091 (0.963–1.238)	1.142 (1.008–1.293)	1.383 (1.215–1.575)	< 0.001
Asthma					
Crude	1 (Ref)	1.083 (0.958–1.225)	1.174 (1.033–1.335)	1.509 (1.324–1.721)	< 0.001
Model 1	1 (Ref)	1.134 (0.999–1.288)	1.215 (1.064–1.388)	1.541 (1.349–1.760)	< 0.001
Model 2	1 (Ref)	1.083 (0.950–1.233)	1.094 (0.949–1.261)	1.267 (1.096–1.465)	0.002
Chronic bronchitis					
Crude	1 (Ref)	1.326 (1.089–1.614)	1.730 (1.402–2.134)	2.648 (2.165–3.239)	< 0.001
Model 1	1 (Ref)	1.261 (1.034–1.536)	1.537 (1.241–1.904)	2.226 (1.805–2.746)	< 0.001
Model 2	1 (Ref)	1.147 (0.942–1.396)	1.258 (1.008–1.570)	1.568 (1.263–1.946)	< 0.001
COPD					
Crude	1 (Ref)	1.521 (1.048–2.207)	2.199 (1.500-3.223)	3.934 (2.743–5.642)	< 0.001
Model 1	1 (Ref)	1.180 (0.811–1.716)	1.586 (1.076–2.339)	2.704 (1.868–3.914)	< 0.001
Model 2	1 (Ref)	1.116 (0.765–1.629)	1.340 (0.915–1.964)	1.907 (1.311–2.774)	< 0.001

Abbreviations IBI, inflammatory burden index; CIAD, chronic inflammatory airway disease; COPD, chronic obstructive pulmonary disease; PIR, poverty income ratio; HEI-2015, Healthy Eating Index 2015; CCI, Charlson Comorbidity Index. Data are presented as OR (95% CI) unless indicated otherwise. Model 1: Adjusted for age (40–59, or ≥ 60 years), sex (female, or male), and race/ethnicity (non-Hispanic White, non-Hispanic Black or other race); Model 2: Model 1 + living status (with partners, or alone), education level (below high school, high school, or above high school), family PIR (< 1.0, or ≥ 1.0), BMI (< 25.0, 25.0-29.9, or > 29.9 kg/m^2), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficiently active, or active), HEI (in quartiles), and CCI (continous)

other inflammatory markers, a positive correlation was noted between CRP levels and the prevalence of CIAD, asthma, chronic bronchitis, and COPD, as well as between neutrophil counts and the prevalence of CIAD, chronic bronchitis, and COPD. Moreover, a positive correlation was established between leukocyte counts and the prevalence of COPD (Table S3).

Associations between IBI and mortality among participants with CIAD

During the median follow-up period of 12.33 (95%CI, 9.92-16.00) years, there were 1221 deaths from all causes and 220 deaths from respiratory disease among 4499 participants with CIAD. Kaplan-Meier survival curves showed that, across quartiles of IBI, participants in the highest quartile had the highest risk of all-cause death and respiratory disease mortality (Fig. 1). After multivariate adjustments, the fourth quartile remained significantly associated with an increased risk of all-cause mortality (HR = 2.227, 95% CI 1.714–2.893) and respiratory disease mortality (HR = 2.748, 95% CI 1.383–5.459) compared to the first quartile of IBI (Table 3). In addition, linear associations were observed between IBI and the risk of all-cause mortality (*P* for nonlinearity = 0.358, Fig. 2A) and respiratory disease mortality (P for nonlinearity = 0.446, Fig. 2B). In addition, individuals with elevated CRP and neutrophil counts demonstrated the highest probability of all-cause mortality and respiratory disease mortality, as shown in Figure S3A, B, D, and E. Conversely, those in the lowest quartile of leukocyte counts showed the highest risk of all-cause death and respiratory disease mortality (Figure S3C, F). After adjusting for multiple variables, the fourth quartile of CRP and neutrophil counts showed a significant association with a higher risk of mortality from all causes and respiratory

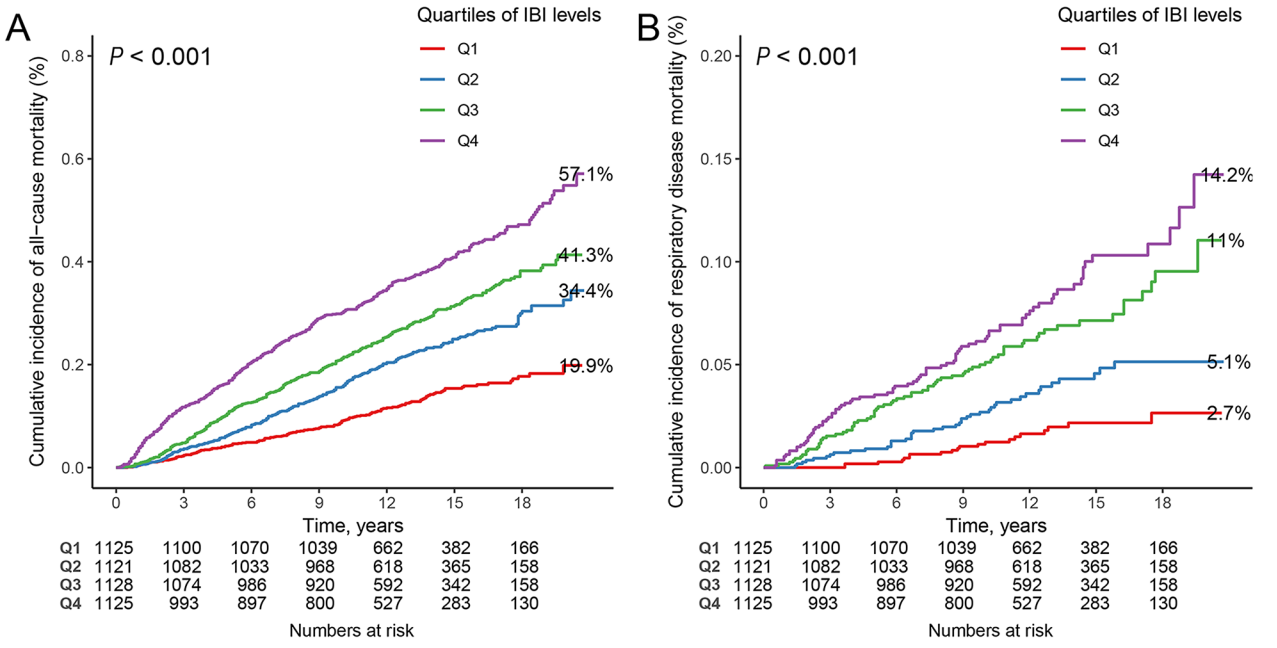

Fig. 1 Kaplan-Meier survival curves for quartiles of inflammatory burden index (IBI) and all-cause and respiratory disease mortality in participants with CIAD in NHANES 2001–2010. (**A**) IBI and all-cause mortality; (**B**) IBI and respiratory disease mortality

Table 3 COX regression analysis of quartiles of IBI levels with all-cause and respiratory disease mortality among participants with CIAD in NHANES 2001–2010 ($n = 4,499$)

	Quartiles of IBI levels				
	< 0.19	**0.19–0.53**	**0.54–1.41**	**> 1.41**	P_{trend}
All-cause mortality					
Crude	1 (Ref)	1.748 (1.336–2.286)	2.418 (1.898–3.082)	4.044 (3.255–5.026)	< 0.001
Model 1	1 (Ref)	1.338 (1.019–1.756)	1.684 (1.322–2.145)	2.619 (2.075–3.306)	< 0.001
Model 2	1 (Ref)	1.381 (1.046–1.824)	1.647 (1.275–2.127)	2.227 (1.714–2.893)	< 0.001
Respiratory disease mortality					
Crude	1 (Ref)	2.013 (1.021–3.970)	3.961 (2.245–6.986)	5.287 (2.890–9.669)	< 0.001
Model 1	1 (Ref)	1.462 (0.734–2.912)	2.513 (1.375–4.593)	3.062 (1.630–5.751)	< 0.001
Model 2	1 (Ref)	1.606 (0.812–3.176)	2.615 (1.399–4.889)	2.748 (1.383–5.459)	0.007

Abbreviations IBI, inflammatory burden index; CIAD, chronic inflammatory airway disease; PIR, poverty income ratio; HEI-2015, Healthy Eating Index 2015; CCI, Charlson Comorbidity Index. Data are presented as HR (95% CI) unless indicated otherwise. Model 1: Adjusted for age (40–59, or ≥ 60 years), sex (female, or male), and race/ethnicity (non-Hispanic White, non-Hispanic Black or other race); Model 2: Model 1 + living status (with partners, or alone), education level (below high school, high school, or above high school), family PIR (< 1.0, or ≥ 1.0), BMI (< 25.0, 25.0-29.9, or > 29.9 kg/m^2), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficiently active, or active), HEI (in quartiles), and CCI (continous)

diseases. In contrast, the fourth quartile of leukocyte count did not exhibit a significant association with an increased risk of mortality from all causes and respiratory diseases (Table S4).

Predictive and capability value of IBI for all-cause and respiratory disease mortality in CIAD

Time-dependent ROC analysis was performed to assess the prognostic significance of IBI for all-cause and respiratory disease mortality in CIAD. The results showed that the area under the curves (AUCs) for IBI were 0.703, 0.669, 0.651, and 0.633 for the 3-year, 5-year, 10-year, and 15-year all-cause mortality, respectively (Fig. 3A). The AUCs for IBI were 0.765, 0.735, 0.675, and 0.668 for the 3-year, 5-year, 10-year, and 15-year respiratory disease mortality, respectively (Fig. 3B). In comparison to IBI, the AUCs for CRP, neutrophil counts, and leukocyte counts were lower across the 3-year, 5-year, 10-year, and 15-year periods for both all-cause and respiratory disease mortality (**Figure S4**). These results indicated that IBI had valid predictive value for both short-term and long-term all-cause and respiratory disease mortality. Spearman correlation analysis revealed a robust association between IBI and CRP levels (Fig. 4A). Additionally, a variable importance analysis using a random survival forest model underscored the pivotal role of IBI in predicting

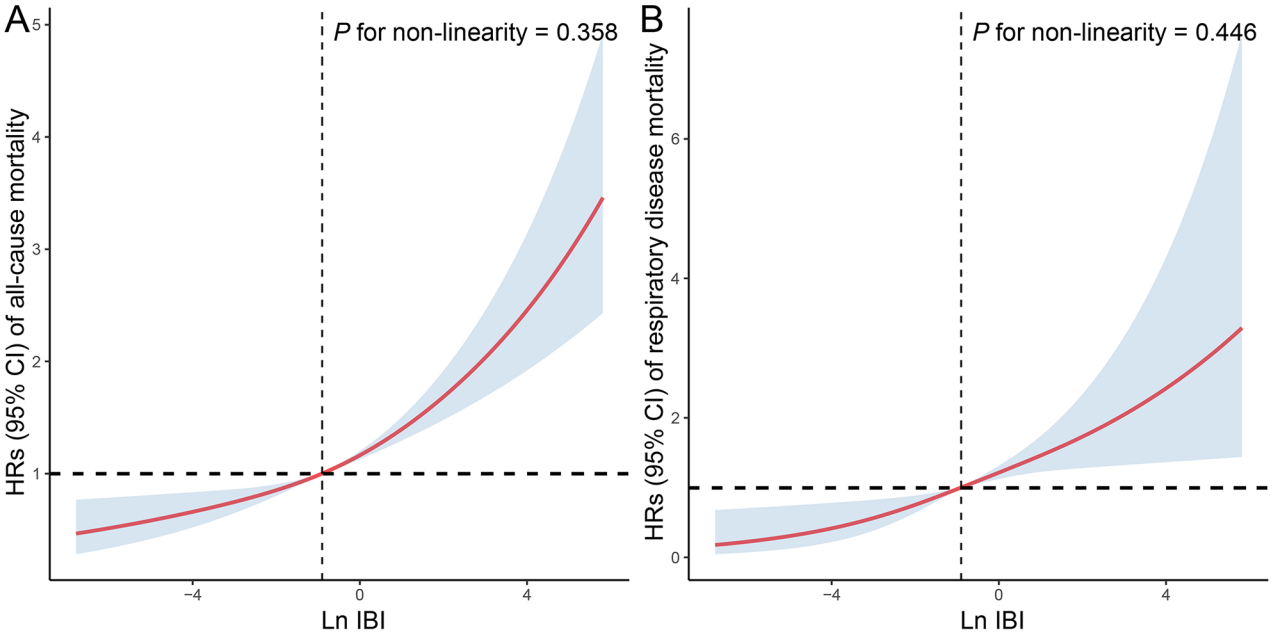

Fig. 2 The exposure-response association of IBI with all-cause (**A**) and respiratory disease (**B**) mortality by restricted cubic spline (RCS). Analyses were adjusted for age (20–39, 40–59, or ≥ 60 years), sex (female, or male), race/ethnicity (non-Hispanic White, non-Hispanic Black or other race), living status (with partners, or alone), education level (below high school, high school, or above high school), family PIR (< 1.0, or ≥ 1.0), BMI (< 25.0, 25.0-29.9, or > 29.9 kg/m2), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficiently active, or active), HEI (in quartiles), and CCI (continous)

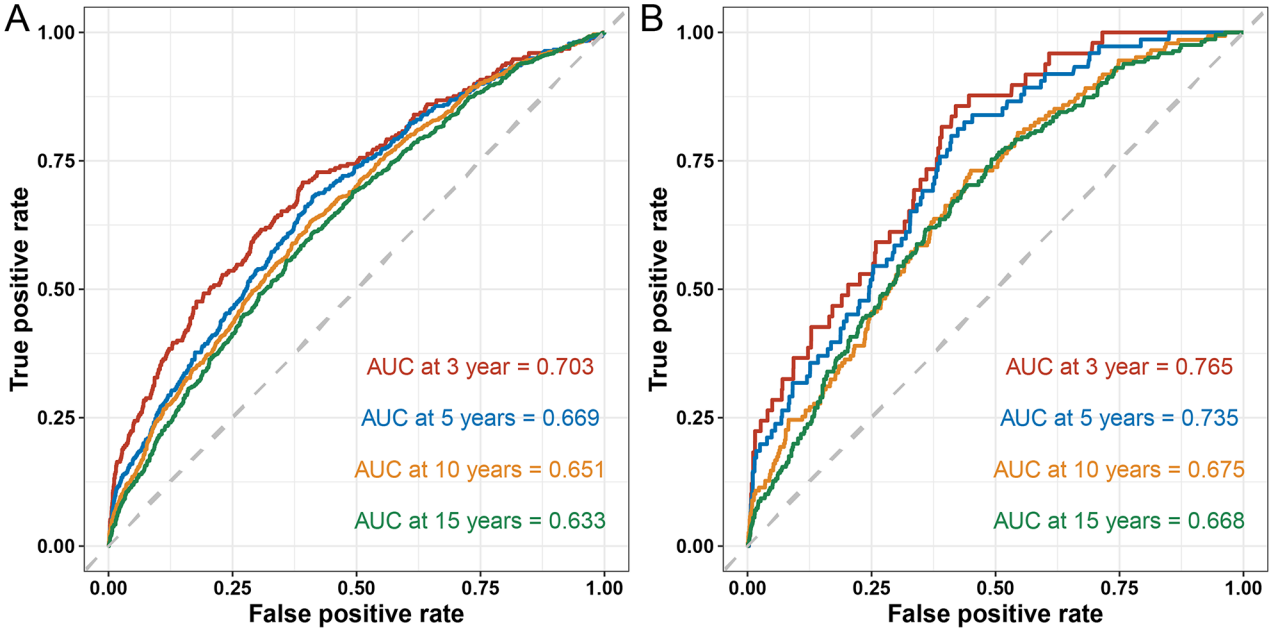

Fig. 3 Time-dependent ROC curves assessing the predictive capability of IBI for all-cause (**A**) and respiratory disease (**B**) mortality at 3, 5, 10, and 15 years

mortality from all-cause and respiratory diseases. Among the IBI and its components, the predictive value of IBI was the highest for all-cause and respiratory disease mortality (Fig. 4B and C).

Subgroup analysis

To deepen our comprehension of the relationship between IBI and all-cause mortality across diverse variables, we conducted subgroup analyses stratified by age, sex, race, living status, education level, family PIR, smoking status, drinking status, BMI, physical activity, and

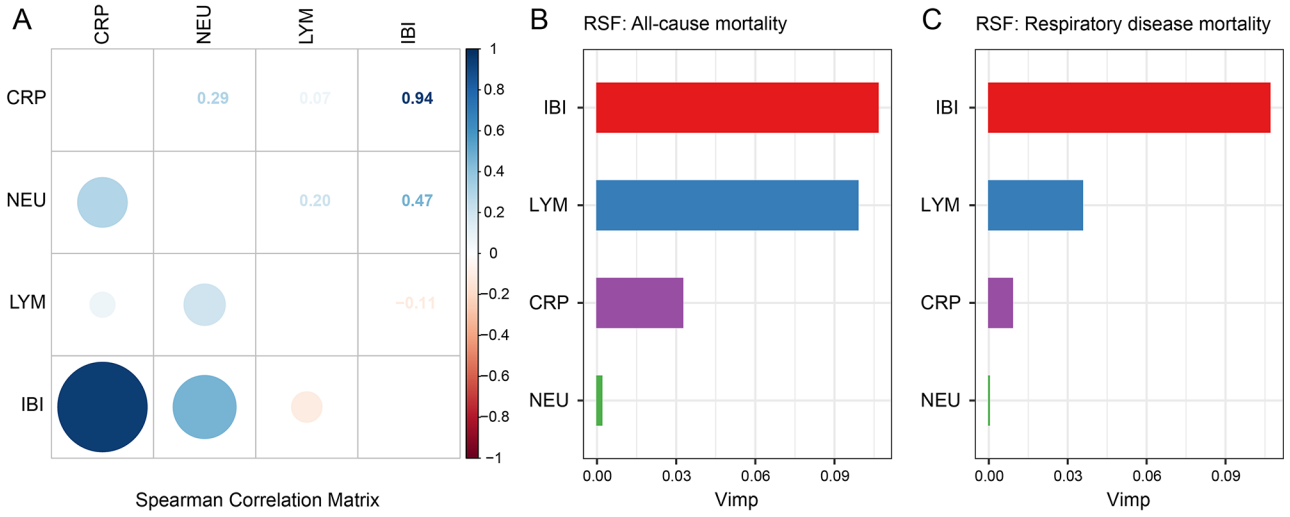

Fig. 4 Capability of inflammatory burden index (IBI) and its components to predict all-cause and respiratory disease mortality. (**A**) Spearman's correlation analysis was used to calculate the correlation coefficients among IBI and its components; (**B**) Ranking the significance of the IBI and its components in predicting all-cause mortality using random survival forest; (**C**) Ranking the significance of the IBI and its components in predicting respiratory disease mortality using random survival forest

HEI groups (Table 4). Across most subgroups, higher quartiles of IBI levels consistently demonstrated an augmented risk of all-cause mortality. Particularly noteworthy are the findings across age groups 20–39, 40–59, and ≥60 years, where the fourth quartile exhibited significant associations with increased all-cause mortality, with HRs of 4.109 (95% CI: 1.223–13.803), 3.038 (95% CI: 1.819–5.075), and 1.810 (95% CI: 1.371–2.389), respectively. The relationship between IBI levels and all-cause mortality among individuals with CIAD manifests differing degrees of significance across age strata, notably showing a more pronounced effect in younger age groups (*P* for interaction=0.011), where elevated IBI levels correlate with markedly heightened mortality risk.

Sensitivity analysis

We conducted four sensitivity analyses to validate our findings. Higher IBI quartiles were significantly associated with increased all-cause and respiratory disease mortality among participants with asthma (Table S5) and those with chronic bronchitis or COPD (Table S6). Excluding participants who died within two years of follow-up did not alter the association between higher IBI levels and increased mortality in CIAD patients (Table S7). Additionally, adjusting for respiratory agents confirmed the significant association between higher IBI levels and mortality among CIAD participants (Table S8). These analyses affirm the robustness of our results.

Discussion

The major finding of the current study was that a higher IBI was associated with an increased prevalence of total and specific CIAD (including asthma, chronic bronchitis, and COPD), as well as an increased risk of all-cause and respiratory disease mortality in adults with CIAD after adjusting for multiple confounders. Our analysis further demonstrated great predictive performance of IBI for both short-term and long-term risks of all-cause and respiratory disease mortality. Moreover, when compared to traditional inflammatory markers such as CRP, neutrophil counts, and leukocyte counts, IBI demonstrated superior predictive capability for assessing the risk of all-cause and respiratory disease mortality. These findings suggested that IBI might serve as a more sensitive and specific biomarker for identifying individuals at high risk for mortality due to overall-cause and respiratory diseases. These results further supported the connection between chronic inflammation, CIAD pathogenesis, and mortality. Additionally, our subgroups analysis revealed a consistent association between quartiles of IBI levels and all-cause mortality in CIAD patients, irrespective of various potential confounders including sex, race/ethnicity, living status, educational level, family income, BMI, smoking habits, alcohol consumption, physical exercise, HEI-2015. However, the associations between IBI and all-cause mortality varied among different age groups, with the hazard ratio seemingly higher in younger populations. A stronger association was observed between IBI and the risk of all-cause mortality in the 20–39 years and 40–59 years groups compared to the ≥60 years group. This finding highlighted the importance of early identification and management of systemic inflammation and immune response in individuals with CIAD, especially in the age group of 20–59 years old.

Chronic inflammation has been associated with a range of chronic diseases, including cardiovascular diseases,

Table 4 Stratified analyses of the associations between quartiles of IBI levels and all-cause mortality among participants with CIAD in NHANES 2001–2010 ($n = 4,499$)

Subgroups	N	Quartiles of IBI levels				$P_{interaction}$
		< 0.19	0.19–0.53	0.54–1.41	> 1.41	
Age, years						0.011
20–39	1423	1 (Ref)	1.241 (0.278–5.542)	1.615 (0.386–6.749)	4.109 (1.223–13.803)	
40–59	1423	1 (Ref)	1.532 (0.846–2.774)	1.662 (0.919–3.007)	3.038 (1.819–5.075)	
≥ 60	1653	1 (Ref)	1.288 (0.972–1.707)	1.482 (1.151–1.907)	1.810 (1.371–2.389)	
Sex, %						0.235
Female	2580	1 (Ref)	1.361 (0.857–2.162)	1.909 (1.203–3.032)	2.813 (1.791–4.419)	
Male	1919	1 (Ref)	1.384 (0.962–1.991)	1.463 (1.066–2.007)	1.930 (1.349–2.759)	
Race, %						0.558
Non-Hispanic White	2593	1 (Ref)	1.347 (0.976–1.857)	1.537 (1.138–2.076)	2.216 (1.638–2.999)	
Non-Hispanic Black	912	1 (Ref)	1.431 (0.757–2.704)	2.121 (1.312–3.427)	2.116 (1.266–3.538)	
Other	994	1 (Ref)	1.587 (0.734–3.435)	2.625 (1.325–5.203)	2.538 (1.200-5.367)	
Living status, %						0.126
Alone	2021	1 (Ref)	1.070 (0.797–1.437)	1.212 (0.897–1.637)	1.825 (1.369–2.435)	
With partners	2478	1 (Ref)	1.828 (1.191–2.805)	2.242 (1.495–3.360)	2.712 (1.774–4.147)	
Education level, %						0.172
Below high school	1301	1 (Ref)	1.019 (0.689–1.506)	1.476 (1.041–2.091)	1.751 (1.237–2.478)	
High school	1072	1 (Ref)	1.944 (1.113–3.393)	1.855 (1.145–3.006)	3.436 (2.041–5.783)	
Above high school	2126	1 (Ref)	1.465 (0.917–2.340)	1.651 (1.024–2.661)	2.201 (1.359–3.564)	
Family PIR, %						0.691
≤ 1.0	1017	1 (Ref)	1.382 (0.898–2.127)	1.853 (1.194–2.875)	2.533 (1.615–3.973)	
1.1–3.0	1921	1 (Ref)	1.220 (0.878–1.696)	1.380 (0.994–1.914)	1.892 (1.363–2.628)	
> 3.0	1561	1 (Ref)	1.594 (0.922–2.758)	2.068 (1.149–3.723)	2.746 (1.498–5.035)	
Smoking status, %						0.290
Never smoker	1896	1 (Ref)	1.263 (0.796–2.004)	2.005 (1.271–3.162)	2.730 (1.739–4.285)	
Former smoker	1344	1 (Ref)	1.420 (1.004–2.010)	1.243 (0.861–1.793)	2.005 (1.396–2.880)	
Current smoker	1259	1 (Ref)	1.512 (0.928–2.464)	2.007 (1.318–3.055)	2.443 (1.555–3.840)	
Drinking status, %						0.086
Nondrinker	998	1 (Ref)	1.282 (0.844–1.948)	1.490 (1.005–2.208)	1.931 (1.304–2.860)	
Low-to-moderate drinker	3098	1 (Ref)	1.446 (1.019–2.052)	1.732 (1.268–2.366)	2.180 (1.558–3.052)	
Heavy drinker	403	1 (Ref)	1.101 (0.409–2.960)	1.832 (0.702–4.781)	4.533 (1.725–11.912)	
Body mass index, %						0.791
< 25.0 kg/m^2	1253	1 (Ref)	1.509 (1.055–2.159)	1.427 (0.983–2.072)	1.890 (1.301–2.745)	
25.0–29.9 kg/m^2	1343	1 (Ref)	1.314 (0.842–2.053)	1.886 (1.179–3.019)	2.501 (1.608–3.889)	
> 29.9 kg/m^2	1903	1 (Ref)	1.246 (0.645–2.405)	1.442 (0.753–2.761)	2.123 (1.132–3.982)	
Physical activity, %						0.273
Inactive	1444	1 (Ref)	1.453 (1.059–1.993)	1.432 (1.048–1.956)	1.889 (1.351–2.640)	
Insufficiently active	1710	1 (Ref)	1.489 (0.858–2.586)	1.868 (1.053–3.314)	2.610 (1.525–4.468)	
Active	1345	1 (Ref)	0.969 (0.586–1.603)	1.358 (0.899–2.051)	2.079 (1.423–3.038)	
HEI, %						0.998
Q1	1125	1 (Ref)	1.378 (0.774–2.455)	1.707 (0.999–2.918)	2.477 (1.474–4.163)	
Q2	1125	1 (Ref)	1.311 (0.762–2.257)	1.726 (1.057–2.819)	2.392 (1.397–4.096)	
Q3	1124	1 (Ref)	1.429 (0.939–2.175)	1.516 (1.029–2.233)	2.149 (1.421–3.250)	
Q4	1125	1 (Ref)	1.293 (0.760–2.199)	1.592 (0.905–2.799)	2.018 (1.193–3.412)	

Abbreviations IBI, inflammatory burden index; CIAD, chronic inflammatory airway disease; PIR, poverty income ratio; HEI-2015, Healthy Eating Index 2015; CCI, Charlson Comorbidity Index. Analyses were adjusted for covariates age (20–39, 40–59, or ≥ 60 years), sex (female, or male), race/ethnicity (non-Hispanic White, non-Hispanic Black or other race), living status (with partners, or alone), education level (below high school, high school, or above high school), family PIR (< 1.0, or ≥ 1.0), BMI (< 25.0, 25.0-29.9, or > 29.9 kg/m2), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficiently active, or active), HEI (in quartiles), and CCI (continous) when they were not the strata variables

diabetes, cancer, and respiratory diseases [30]. Persistent inflammation in the respiratory tract is fundamental to the development of various pulmonary diseases such as chronic obstructive pulmonary disease and asthma [31, 32]. Chronic inflammation in tissues often triggers the recruitment of immune cells from the bloodstream, intensifying the inflammatory reaction. Asthma is characterized by environmental triggers that activate dendritic cells and airway epithelial cells, leading to the initiation of a Th2 immune response [33, 34]. This cascade results in the release of mediators and cytokines from mast cells, basophils, and neutrophils, ultimately increasing eosinophil adhesion [35–37]. Elevated levels of inflammatory markers, such as white blood cell count, eosinophil count, and lymphocyte ratio, have been reported in several studies to be associated with asthma severity [34, 38]. Ke et al. also revealed a significant association between inflammatory biomarkers derived from complete blood cell counts and a heightened likelihood of all-cause and respiratory disease mortality in adults with asthma [18]. COPD is a progressive inflammatory lung disease with strong links to smoking [39]. The dysregulation of the immune system due to exposure to cigarette smoke results in persistent and heightened inflammation in the lungs, a crucial factor in the development of COPD [40]. Alveolar macrophages are considered central players in the perpetuation of inflammation in COPD, as they release chemokines that attract neutrophils, lymphocytes, and to the bronchial epithelium [41]. Lee et al. observed in a prospective study that the neutrophil to lymphocyte ratio was a reliable biomarker for forecasting COPD exacerbations and subsequent respiratory hospitalizations in individuals with COPD [42]. Paliogiannis et al. reviewed prior research and emphasized the utility of the neutrophil to lymphocyte ratio as a direct and valuable marker for predicting acute exacerbations of COPD as well as mortality [43]. In addition, higher systemic immune-inflammation index (SII) levels are independently associated with an increased likelihood of COPD and higher all-cause mortality rates among COPD patients [44]. Here, a question arises as to whether there exists another inflammation index that, when combined with these traditional markers, could effectively assess CIAD, including asthma and COPD.

A novel composite of inflammatory markers, known as IBI, was first introduced by Xie as a method to assess the inflammatory load in various types of cancer and forecast patient outcomes [23]. It had been demonstrated that IBI can differentiate the prognosis of cancer patients with different levels of inflammation and also provides significant prognostic stratification for most cancer patients [24–27]. However, the relationship between IBI and both the prevalence of CIAD and the risk of mortality in patients with CIAD had yet to be determined. In this study, we firstly showed that a higher IBI is independently associated with an increased prevalence of total and specific CIAD (asthma, chronic bronchitis, and COPD), as well as an increased risk of all-cause and respiratory disease mortality in adults with CIAD. These findings suggested that IBI monitoring can act as a point of reference for disease monitoring and prognosis assessment. Our variable importance analysis, conducted using a random survival forest model, further revealed that IBI had the highest predictive value for both all-cause and respiratory disease mortality when compared to conventional inflammatory markers such as CRP, neutrophil counts, and lymphocyte counts. The integration of CRP and NLR forms the IBI. CRP serves as a marker for inflammatory processes, while NLR indicates immune response equilibrium. Through the integration of these markers, the IBI offers a thorough evaluation of systemic inflammation (CRP) and immune response equilibrium (NLR), thereby providing a more comprehensive perspective on an individual's health. The present investigation illustrates that enhancing the inclusivity of CRP and NLR within the IBI enhances its prognostic precision in assessing the risk of all-cause and respiratory disease mortality. The framework of IBI acknowledges the complex interplay of inflammation and immune responses, taking into account individual variability. This individualized approach shows potential in precisely identifying individuals at a heightened vulnerability to adverse health outcomes.

The major advantage of this study was its utilization of a large, nationally representative sample, which facilitated the investigation of the association between IBI and the prevalence of CIAD and mortality in adults with CIAD. This aspect enhanced the generalizability of the findings to the wider population in the United States. Secondly, our study accounted for several key factors influencing lung function, such as age, smoking, physical activity, BMI, and other confounding variables, in the analysis. Our findings consistently showed stability even after accounting for these confounding factors. Thirdly, we utilized a variable importance analysis using a random survival forest model, emphasizing the critical role of IBI in predicting mortality from both all-cause and respiratory diseases. Finally, in contrast to previous research, our study examined the association between IBI and the risk of all-cause and respiratory disease mortality among individuals with CIAD. The study's findings suggests that IBI could serve as a valuable prognostic biomarker. Elevated IBI levels might help identify individuals at higher risk for CIAD and related mortality, facilitating earlier interventions and tailored management. Additionally, the strong link between higher IBI levels and increased all-cause and respiratory disease mortality highlights the need for aggressive management of systemic

inflammation in CIAD patients. This could involve optimizing anti-inflammatory treatments, managing comorbid conditions, and promoting lifestyle changes such as smoking cessation, regular physical activity, and a healthy diet.

There are various limitations inherent in this study. Firstly, the observational design limits our ability to establish a causal relationship between the IBI and the risk of CIAD as well as mortality in individuals with CIAD. While we observed associations, causality cannot be inferred due to the potential for residual confounding and the inherent limitations of observational data. Secondly, the reliance on self-reported data for the assessment of CIAD introduces the possibility of recall bias. Participants may misreport or fail to accurately recall their medical history, which can lead to misclassification and potentially biased estimates of the associations between IBI and CIAD outcomes. This self-reporting bias is a common concern in epidemiological studies and may affect the robustness of our findings. Thirdly, although we utilized data from the NHANES 1999–2010, pulmonary function test data were only available for the NHANES 2007–2012. The substantial missing data precluded a comprehensive analysis of baseline lung function, limiting our ability to fully assess its impact on the relationship between the IBI and CIAD. Fourthly, even after adjusting for multiple potential confounding factors, the study was unable to completely eliminate the possibility of residual confounding. Finally, Single-point measurements for CRP, neutrophils, and lymphocytes were used in this study, which can vary over time due to transient factors like acute infections. This approach may lead to variability and potential bias, affecting the reliability of our findings. Therefore, while our results show significant associations, caution is needed in interpretation. Future studies using longitudinal data could provide a more comprehensive understanding of how these biomarkers relate to CIAD. Additionally, efforts should be made to develop and validate more refined inflammatory indices by incorporating additional biomarkers and clinical variables, thereby enhancing their accuracy and predictive power.

Conclusion

Our findings suggest that higher IBI is associated with a higher prevalence of CIAD (including asthma, chronic bronchitis, and COPD). Among participants with CIAD, higher IBI is associated with an increased risk of all-cause and respiratory disease mortality. As a novel inflammatory biomarker, IBI can be used to predict the risk of CIAD and mortality, and it demonstrates superiority compared to CRP, neutrophil count, and leukocyte count. Further research is required to validate these findings and investigate the mechanisms connecting IBI and CIAD.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03211-6.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
N.Z. and S.L. designed the study. L.W. and X.K. performed the statistical analyses. N.Z., S.L., W.H. and C.C. drafted the manuscript. W.H. and C.C. critically reviewed the manuscript. All authors read and approved the fnal manuscript.

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Data availability
The datasets analyzed during the current study are publicly available in the National Health Nutrition Survey (NHANES), https://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate
This study was approved by the NCHS Research Ethics Review Board (ERB) and followed the ethical standards for human research. The details of the NCHS Research Ethics Review Board Approval can be found on the NHANES website (https://www.cdc.gov/nchs/nhanes/irba98.htm). No written informed consent was needed for this study according to the national and institutional regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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