ORIGINAL RESEARCH

Inverted U-Shaped relationship Between Systemic Immune-Inflammation Index and Pulmonary Function: A Large Population-Based Study in US Adults

Qian Yuan*, Long-Wu Xiao*, Yao Zhang, Long Li, Teng Xia, Qing Xu, Shi-Gui Xing 🔟, Liu-Shun Wang

Department of Thoracic Surgery, Nan Jing Gaochun PEople's Hospital (The Gaochun Affiliated Hospital of Jiang Su University), Nanjing, Jiangsu, 210000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Shi-Gui Xing; Liu-Shun Wang, Email gcxw5988@163.com; lswang052066@sina.com

Background: Systemic immune-inflammation index (SII) is a novel comprehensive inflammatory marker. Inflammation is associated with impaired lung function. We aimed to explore the possible relationship between SII and lung function to examine the potential of SII in predicting lung function decline.

Methods: A cross-sectional survey was conducted using the data of the NHANES from 2007 to 2012. Multiple linear regression models were used to analyze the linear relationship between SII and pulmonary functions. Sensitivity analyses, subgroup analyses, and interaction tests were used to examine the robustness of this relationship across populations. Fitted smooth curves and threshold effect analysis were used to describe the nonlinear relationships.

Results: A total of 10,125 patients were included in this study. After adjusting for all covariates, multiple linear regression model analysis showed that high Log2-SII level was significantly associated with decreased FVC(β, −23.4061; 95% CI, −42.2805- −4.5317), FEV1(β, −46.7730; 95% CI, −63.3371- −30.2089), FEV1%(β, −0.7923; 95% CI, −1.1635- −0.4211), FEV1/FVC(β, −0.6366; 95% CI, −0.8328- −0.4404) and PEF(β, −121.4468; 95% CI,-164.1939- −78.6998). The negative correlation between Log2-SII and pulmonary function indexes remained stable in trend test and stratified analysis. Inverted U-shaped relationships between Log2-SII and FVC, FEV1, FEV1%, and PEF were observed, while a negative linear correlation existed between FEV1/FVC and Log2-SII. The cutoff values of the nonlinear relationship between Log2-SII and FVC, FEV1, FEV1%, PEF were 8.3736, 8.0688, 8.3745, and 8.5255, respectively. When SII exceeded the critical value, the lung function decreased significantly.

Conclusion: This study found a close correlation between SII and pulmonary function indicators. This study investigated the SII threshold when lung functions began to decline in the overall population. SII may become a promising serological indicator for predicting lung function decline. However, prospective studies were needed further to establish the causal relationship between these two factors.

Keywords: NHANES, population-based study, systemic immune-inflammation index, pulmonary function

Introduction

Chronic respiratory diseases (CRD), including chronic obstructive pulmonary disease (COPD), asthma, and lung cancer, are a group of diseases that affect the health of the lungs and trachea.[1,2] CRD is one of the leading causes of death worldwide and a major global public health problem.[3]

Pulmonary function test is of great value for the diagnosis of respiratory diseases and the evaluation of therapeutic effect. International guidelines have forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV1) as parameters, such as chronic obstructive pulmonary disease (COPD), interstitial lung disease, asthma, and respiratory

system disease diagnostic criteria.[4] Early and dynamic pulmonary function assessment is an effective means of early screening for chronic respiratory diseases, which helps to take targeted intervention measures before the progression of lung disease.[5] However, pulmonary function examination is not used as routine screening at all levels of medical and health care institutions worldwide, and most patients will undergo pulmonary function examination only when they have severe symptoms. At the same time, there are also some contraindications for pulmonary function testing,[6] such as myocardial infarction, massive hemoptysis, shock patients, etc. Pulmonary function testing plays an important role in the perioperative assessment, treatment, and prognosis of thoracic surgery patients. However, within 3 weeks after thoracic surgery, pulmonary function testing is also contraindicated. There is a lack of effective means of dynamic detection of lung function in patients with these conditions.[7]

To sum up, finding a simple and effective biomarker to evaluate lung function is particularly important for early detection of lung function decline and timely prevention of further progression of impaired lung function.

COPD is characterized by chronic bronchitis, chronic airway obstruction, airway remodeling, and emphysema, resulting in a progressive, irreversible decline in lung function.[8] A large number of studies[9] have shown that chronic respiratory diseases such as COPD are related to chronic airway inflammation, which is the core of chronic respiratory diseases. Inflammatory mediators and destructive enzymes released by inflammatory cells, especially infiltrating immune cells, play an irreplaceable role in the destruction of lung tissue and the progressive decline of lung function. Accelerated decline in lung function increases the risk of chronic obstructive pulmonary disease (COPD), and smoking contributes to accelerated decline in lung function and the formation of COPD by increasing lung inflammation.[10] Previous studies have shown that nutrients such as omega-3 fatty acids, which have anti-inflammatory properties, have a certain protective effect on lung function decline.[11]

Previous studies have also shown that single inflammatory cells such as white blood cells and neutrophils are associated with impaired lung function.[12] However, at present, there is a lack of large-scale population studies on the relationship between comprehensive inflammatory indicators and lung function.

The Systemic Immunoinflammatory Index (SII) is a new index based on lymphocyte, neutrophil, and platelet counts. More and more evidences show that SII is a comprehensive indicator reflecting the immune and inflammatory state of the whole body system.[13] At present, a large number of studies have confirmed that SII has a high prognostic value in tumors and chronic diseases caused by chronic inflammation or immune dysfunction, such as lung cancer,[14,15] gastroesophageal adenocarcinoma,[16,17] liver cancer,[18] and cardiovascular and cerebrovascular diseases.[19] SII can be analyzed with readily available data in blood routine, which is economical, convenient, and widely applicable, and may have potential predictive value for lung function decline. However, the relationship between SII and lung function in the population is still unclear.

The National Health and Nutrition Examination Survey (NHANES) is a population-based, cross-sectional survey designed to gather information about the health and nutrition of American households.[20] The database uses a complex hierarchical, multistage probabilistic cluster sampling design to represent the entire US population. Therefore, we conducted a cross-sectional study based on large sample data from the NHANES to explore the relationship between SII and various indicators of lung function. The aim is to provide new strategies and recommendations for lung function assessment and protection.

Materials and Methods
Data Sources
The data used in this study were obtained from the NHANES database. The NHANES database, a major program of the National Center for Health Statistics (NCHS) that provides vital health statistics, is unique in that it combines interviews and physical exams. The NHANES database includes demographic information, physical examinations, laboratory tests, and questionnaires to determine the prevalence of major diseases and risk factors for diseases.[21] The data in this study were collected from the NHANES dataset for 3 periods from 2007 to 2012. All data in this study were approved by the Research Ethics Review Committee of the National Center for Health Statistics. All participants signed informed consent forms. Details can be downloaded from the CDC website (www.cdc.gov/nchs/nhanes/tutorials/default.asp).[22]

Study Subjects

The study was based on data from the 2007 to 2012 NHANES survey, as lung function data for these three cycles is complete in the NHANES database. A total of 30442 subjects were included in this study. According to the purpose of the study, the exclusion criteria were: (1) missing SII data (5463). (2) Lack of lung function data (6310). (3) Under 18 years of age (5127). (4) Participants with a pulmonary function data quality rating of C-F (n=463), cancer patients (n=911), heart failure patients (n=191), and demographic data missing (n=1852). Finally, 10,125 participants were included in the study. The process of research population screening is shown in Figure 1.
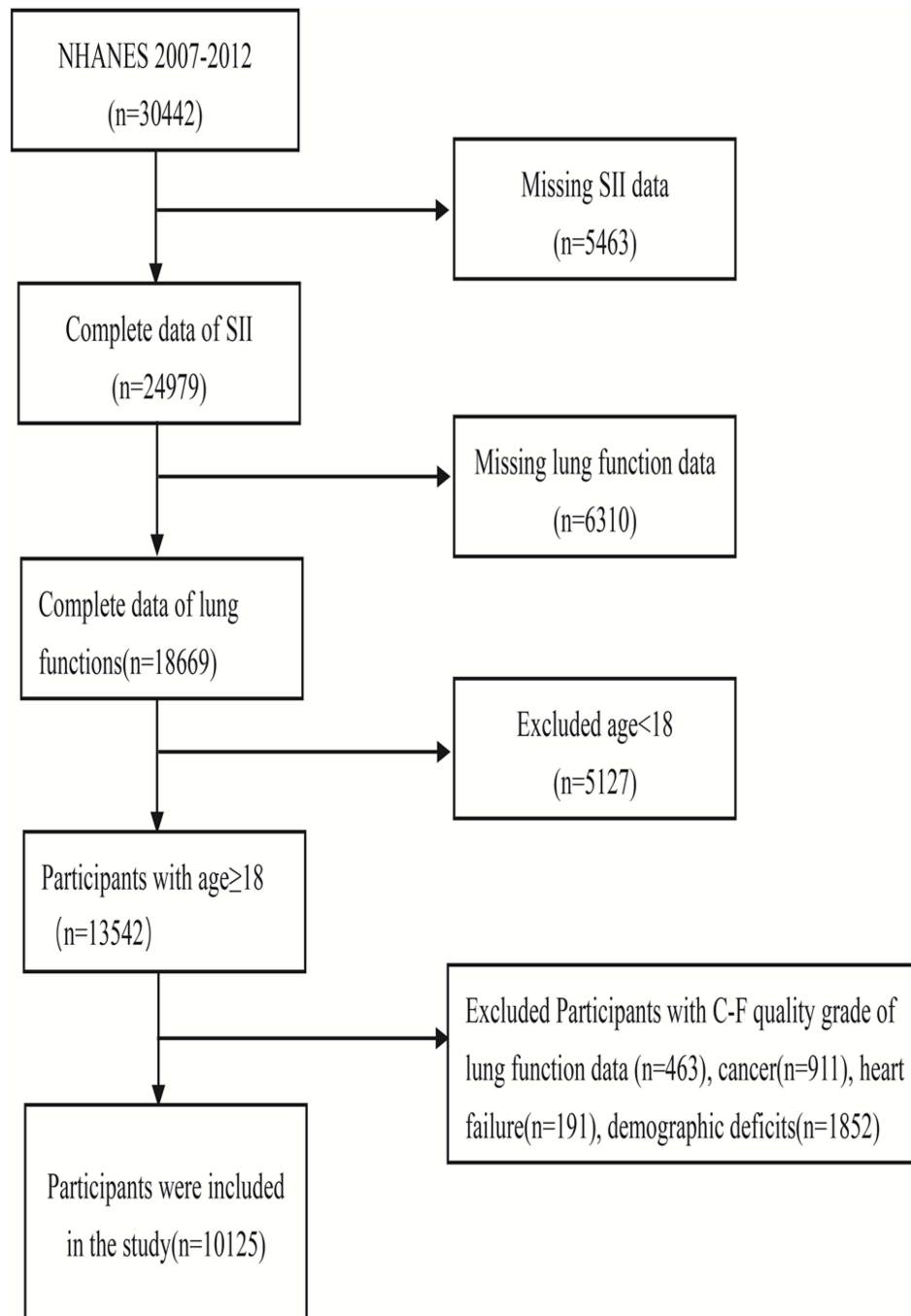

Figure 1 Flow chart of research population selection.

Pulmonary Function

The 2007–2012 NHANES provided spirometry for participants aged 6 to 79 years. The Ohio 822/827 dryroll volume spirometer followed the recommendations from the American Thoracic Society (ATS)/European Respiratory Society (ERS). Ruled out the following participants: chest pain; Physical problems with forced exhalation; Supplemental oxygen; Recent eye surgery, the chest or abdomen; Recent heart attack, stroke, tuberculosis, or coughing up blood. Expert reviewers from the NIOSH Quality Control Center reviewed all the spirometry data collected. To ensure the reliability of the analysis results, we only collected data that were rated as grades A and B in the quality of the spirometric data according to the American Thoracic Society (ATS) standard.[23] The data we mainly used for analysis in this study included FVC, FEV1, FEV1/FVC, and PEF. Higher values for these measures of lung function represent better lung function. We calculated the percentage of predicted FEV1 (FEV1% or FEV1PRE) using the Hankinson equation.[24]

Systemic Immune-Inflammation Index(SII)

SII is calculated according to the complete blood count, and blood sample collection, processing, and quality control are carried out in accordance with the standardization process, The specific experimental methods can be obtained from the NHANES website (https://www.cdc.gov/nchs/nhanes). Lymphocyte, neutrophil, and platelet counts were measured by automated hematology analyzing devices (Coulter® DxH 800 analyzer) and present as $\times 10^3$ cells/ mL. According to previous studies,[25,26] the calculation of SII is based on an accurate formula: SII = platelet count×neutrophil count/ lymphocyte count, which has high clinical application for evaluating the systemic immune and inflammatory status of individuals. In addition, the normality test suggested that the SII data were right-skewed distribution, and in order to ensure the normality of the data, log2 transformation of SII was performed during regression analysis (Figure S1, Table S1).

Covariates

Based on previous studies,[27,28] covariates associated with SII and lung function were included in this study. Age (year), gender, race (Non-Hispanic White, Non-Hispanic Black, Mexican American, Others), BMI (kg/m2), Cotinine (ng/mL), Educational level (less than high school, high school, more than high school), poverty to income ratio (PIR)(<1.5,1.5–3.49,≥3.5), Hypertension history, Diabetes history, Respiratory diseases (asthma, emphysema, and chronic bronchitis). The concentration of cotinine was determined in thirds (Q1, 0.01–0.02ng/mL, Q2, 0.04–0.13 ng/mL, Q3, 27.17–280 ng/mL). Cotinine is an indicator of active and passive smoking and can better reflect an individual's smoking status. The diagnosis of COPD depends on FEV1/FVC<0.7, and the questionnaire: "Have you been told you have chronic obstructive pulmonary disease?

Statistical Analysis

According to the NHANES analysis guidelines and tutorials, sample weights were adjusted in this study (original 2-year sample weights /2).[29] Therefore, we used a Mobile Examination Center (MEC) exam weight (WTMEC2YR) for our analysis, as some of the variables included in this study were collected in MEC. Furthermore, since we combined 3 NHANES survey cycles, the sample weight used in the final analysis is equal to 1/3 of the "WTMEC2YR" value. The influence of weight was fully considered in the subsequent population characteristics analysis and regression analysis. All analyses were based on participants with complete data, and individuals with missing covariate data were excluded from the final analysis. First, the participants were divided into four groups according to the Log2-SII quartile for analysis. Weighted linear regression analysis was used for continuous variables and a design-adjusted Chi-square test was used for categorical variables. In this study, mean ±standard deviation was used to report population characteristics for continuous variables and percentages were used to report population characteristics for categorical variables. Since the influence of sample weights has been adjusted, the specific number of cases was not listed. Multiple linear regression model was used to analyze the relationship between SII and pulmonary function indicators, and the quartile of SII was used as a categorical variable for the trend test (*p* for trend). Three models were used for the analysis: Model 1 did not take into account any confounding variables, Model 2 adjusted for age, sex, and race, and Model 3 took into account the effects of BMI, Cotinine, education, income, history of hypertension, history of diabetes and respiratory diseases on the

basis of the model 2. After fully adjusting for confounding factors, we converted all continuous covariates into categorical variables for hierarchical multiple regression analysis and used the likelihood ratio test to evaluate the interaction effect. Regression coefficient beta values and 95% confidence intervals (CI) were used to describe these results. In this study, a generalized additive model and smooth curve fitting method were used to evaluate the nonlinear relationship between SII and pulmonary function indicators, and the inflection points in the curve were calculated by the non-linear model recursive algorithm to further explore the threshold effect. P<0.05 was considered statistically significant. R (version 2, R Foundation for Statistical Computing, Vienna, Austria) and Empower Stats (version 2.0, Boston, Massachusetts, USA) were used for all statistical analysis.

Results

Baseline Characteristics

A total of 10,125 samples were included in this study. Due to the effect of sample weight, the specific number of cases for categorical variables was not listed in the baseline table The interquartile range of the Log-SII was used for weighted baseline characteristic analysis. The results showed that all variables except cotinine showed significant differences among the four groups. Compared with participants in the lowest quartile, those with higher Log-SII were more likely to be Female, Non-Hispanic White, and have higher BMI, education level, and income level. At the same time, with the increase of Log-SII, the incidence of diabetes, hypertension, and respiratory diseases gradually increased. In particular, FEV1/FVC and PEF decreased gradually with the increase of Log-SII level (Table 1).

The Association Between the SII and Lung Function

Table 2 showed the relationship between SII and lung function in three weighted generalized linear regression models. Since SII was a non-normal distribution, Log2 transformation was performed in the analysis. In the fully adjusted model (Model 3), each

Table 1 Weighted baseline characteristics of all participants stratified by Quartile of Log2-SII

Characteristic	Q1(0.61-8.36)	Q2(8.36-8.83)	Q3(8.83-9.32)	Q4(9.32-14.79)	P-value
Number of subjects (n)	2436	2529	2588	2572	
Age (years)	42.85 ± 15.09	43.15 ± 14.75	43.47 ± 14.40	44.10 ± 14.72	0.0195
Gender (%)					<0.0001
Male	55.77	52.92	49.28	42.95	
Female	44.23	47.08	50.72	57.05	
Race (%)					<0.0001
Non-Hispanic White	60.02	69.23	70.49	73.23	
Non-Hispanic Black	18.19	9.41	8.13	7.51	
Mexican American	9.08	8.58	8.82	7.94	
Others	12.7	12.78	12.55	11.32	
BMI (kg/m2)	27.54 ± 5.88	28.03 ± 6.02	28.88 ± 6.42	29.80 ± 7.49	<0.0001
Cotinine (%)					0.0775
Q1 (0.01-0.02 ng/mL)	37.26	36.26	38.17	34.96	
Q2 (0.04-0.13 ng/mL)	30.82	33.10	30.96	31.42	
Q3 (27.17-280 ng/mL)	31.93	30.64	30.87	33.63	
Educational level (%)					0.0130
Less than high school	17.00	14.95	16.77	15.74	
High school	21.56	20.16	21.72	23.65	
More than high school	61.4	64.89	61.50	60.61	
PIR (%)					0.0037
<1.5	25.82	24.45	25.19	26.20	
1.5-3.49	31.70	28.80	28.18	31.23	
≥3.5	42.82	46.76	46.63	42.57	

(*Continued*)

Table I (Continued).

Characteristic	Q1(0.61-8.36)	Q2(8.36-8.83)	Q3(8.83-9.32)	Q4(9.32-14.79)	P-value
Hypertension history (%)					0.0038
No	76.22	76.25	75.82	72.54	
Yes	23.78	23.75	24.18	27.46	
Diabetes history (%)					0.0027
No	93.34	94.69	93.95	92.23	
Yes	6.66	5.31	6.05	7.77	
Respiratory diseases (%)					0.0002
No	87.49	85.59	83.85	83.41	
Yes	12.51	14.41	16.15	16.59	
FVC (ml)	4238.06 ± 1105.76	4293.22 ± 1097.24	4204.79 ± 1088.86	4056.47 ± 1041.07	<0.0001
FEV1 (ml)	3351.21 ± 921.56	3370.92 ± 896.43	3292.08 ± 877.11	3153.04 ± 854.07	<0.0001
FEV1%	94.36 ± 14.44	95.75 ± 14.15	95.29 ± 14.72	94.14 ± 15.46	<0.0001
FEV1/FVC	79.08 ± 7.43	78.61 ± 7.37	78.46 ± 7.66	77.85 ± 8.59	<0.0001
PEF (ml/s)	8626.45 ± 2229.99	8624.02 ± 2158.85	8491.59 ± 2219.78	8053.35 ± 2035.10	<0.0001
COPD					
No	85.21	84.33	83.22	82.78	
Yes	14.79	15.67	16.78	17.22	

Notes: Q1–Q4: Grouped by quartile according to Log2-SII. Mean ± SD for continuous variables. *P*-value was calculated by weighted linear regression model. (%) for categorical variables . *P* value was calculated by weighted chi-square test.

Table 2 Relationship between SII and lung functions

Log2-SII	Model I	P-value	Model II	P-value	Model III	P-value
	β (95%CI)		β (95%CI)		β(95%CI)	
FVC	-87.7972 (-116.7036,-58.8823)	<0.0001	-46.7615 (-66.0325, -27.4906)	0.000002	-23.4061 (-42.2805, -4.5317)	0.0151
FEV1	-96.2726 (-119.9355, -72.6097)	<0.0001	-65.7233 (-82.6260, -48.8205)	<0.000001	-46.7730 (-63.3371, -30.2089)	<0.0001
FEV1%	-0.1156 (-0.5085, 0.2773)	0.5642	-1.1766 (-1.5517, -0.8015)	<0.000001	-0.7923 (-1.1635, -0.4211)	0.0001
FEV1/FVC	-0.6214 (-0.8294, -0.4134)	<0.0001	-0.6508 (-0.8480, -0.4537)	<0.000001	-0.6366 (-0.8328, -0.4404)	<0.0001
PEF	-264.9141 (-322.6092, -207.2190)	<0.0001	-143.2094 (-186.8636, -99.5552)	<0.000001	-121.4468 (-164.1939, -78.6998)	<0.0001

Notes: Model I: No covariates were adjusted; Model II: Adjusted for sex, age, race; Model III: Adjusted for sex, age, race, BMI, education, PIR, cotinine, diabetes, hypertension, and Respiratory diseases.

one unit increase in Log2-SII was significantly associated with a decrease in FVC(β, −23.4061; 95% CI, −42.2805- −4.5317), FEV1(β, −46.7730; 95% CI, −63.3371- −30.2089), FEV1%(β, −0.7923; 95% CI, −1.1635- −0.4211), FEV1/FVC(β, −0.6366; 95% CI, −0.8328- −0.4404) and PEF(β, −121.4468; 95% CI, −164.1939- −78.6998).

We further converted log2-SII into quartiles for sensitivity analysis. The results showed that the negative correlation between SII and lung function indicators remained stable With the increase of SII, the lung function indexes in each adjusted model showed a gradual downward trend (all *p* for trend<0.001). Compared with participants in the lowest SII quartile, those in the highest quartile had 45.08 decreases in FVC(β, −45.0815; 95% CI, −84.858- −5.305), 92.26 decreases in FEV1(β, −92.2563; 95% CI, −127.164- −57.349), 1.56 decreases in FEV1%(β, −1.5623; 95% CI, −2.3448- −0.7798), 1.23 decreases in FEV1/FVC (β, −1.2348; 95% CI, −1.6487- −0.8209), and 271.45 decreases in PEF(β, −271.4547; 95% CI, −361.489- −181.420) (Table 3).

Subgroup Analysis

To determine the potential interaction of covariates on the association between SII and lung function and the stability of the association between SII and lung function, The study participants were also stratified by age, gender, race, BMI, Cotinine, Educational level, PIR, Hypertension history, Diabetes history and Respiratory diseases for analysis and interaction test. All subgroup analyses were fully adjusted for confounding factors. All covariables except the grouping variable were adjusted. Detailed results of the subgroup analysis are shown in Figures 2–6. SII was negatively correlated

Table 3 Effect of Log2-SII quartiles on lung function indices

	Model I β (95%CI)	Model II β (95%CI)	Model III β (95%CI)
FVC			
Log2-SII quartile categories			
Q1	Ref	Ref	Ref
Q2	55.1528 (-6.4985, 116.8040)	34.8748 (-5.8813, 75.6308)	36.1372 (-3.3720,75.646)
Q3	-33.2726 (-94.3834, 7.8382)	-22.2629 (-62.7701, 18.2443)	-0.8049 (-40.1787,38.569)
Q4	-181.5909 (-242.67,-120.52)	-85.4401 (-126.104,-44.7768)	-45.0815 (-84.858,-5.305)
P for trend	<0.0001	<0.0001	<0.0001
FEV1			
Log2-SII quartile categories			
Q1	Ref	Ref	Ref
Q2	19.7145 (-30.7488, 70.1778)	8.2982 (-27.4541, 44.0505)	8.0008 (-26.6726,42.6743)
Q3	-59.1280 (-109.1489,-9.1071)	-51.2778 (-86.8118, -15.7438)	-35.4813 (-70.0359,-0.927)
Q4	-198.1658 (-248.156,-148.175)	-123.9647 (-159.6357,-88.294)	-92.2563 (-127.164,-57.349)
P for trend	<0.0001	<0.0001	<0.0001
FEV1%			
Log2-SII quartile categories			
Q1	Ref	Ref	Ref
Q2	1.3986 (0.5602, 2.2370)	0.0538 (-0.7398, 0.8475)	0.1102 (-0.6670, 0.8874)
Q3	0.9346 (0.1035, 1.7656)	-0.7898 (-1.5786, -0.0011)	-0.5335 (-1.3081, 0.2411)
Q4	-0.2197 (-1.0503, 0.6108)	-2.2661 (-3.0579, -1.4743)	-1.5623 (-2.3448, -0.7798)
P for trend	0.2540	<0.0001	<0.0001
FEV1/FVC			
Log2-SII quartile categories			
Q1	Ref	Ref	Ref
Q2	-0.4717 (-0.9159, -0.0274)	-0.3463 (-0.7637, 0.0711)	-0.3842 (-0.7953, 0.0269)
Q3	-0.6172 (-1.0576, -0.1768)	-0.6233 (-1.0382, -0.2085)	-0.6580 (-1.0677, -0.2483)
Q4	-1.2337 (-1.6738, -0.7936)	-1.2365 (-1.6529, -0.8200)	-1.2348 (-1.6487, -0.8209)
P for trend	<0.0001	<0.0001	<0.0001
PEF			
Log2-SII quartile categories			
Q1	Ref	Ref	Ref
Q2	-2.4358 (-125.4208,120.5493)	24.9455 (-67.3280, 117.2189)	8.0914 (-81.3391,97.5218)
Q3	-134.8657 (-256.7730,-12.959)	-36.8821 (-128.5921,54.8279)	-36.9450 (-126.0692,52.1791)
Q4	-573.108 (-694.9407,-451.275)	-304.3260 (-396.3895,-212.263)	-271.4547 (-361.489,-181.420)
P for trend	<0.0001	<0.0001	<0.0001

Notes: Model I: No covariates were adjusted; Model II: Adjusted for sex, age, race; Model III: Adjusted for sex, age, race, BMI, education, PIR, cotinine, diabetes, hypertension, and Respiratory diseases. Log2-SII quartile ranges: Q1(0.61-8.36), Q2(8.36-8.83), Q3(8.83-9.32), Q4(9.32-14.79).

with lung function parameters (FVC, FEV1, FEV1%, FEV1/FEVC, PEF) in all subgroup analyses. Although we observed positive β-effect values for FVC in the Non-Hispanic Black population, FEV1 in the population with college degrees or above, and FEV1/FVC in the BMI≥30 population, none of the above results were statistically significant (*p*>0.05), suggesting the robustness of our findings.

The interaction test showed that education level and respiratory diseases may have an impact on the association between SII and FEV1%(p for interaction>0.05). Gender, race, and BMI may have an impact on the correlation between SII and FEV1(p for interaction>0.05). Education level, cotinine concentration, BMI, and history of hypertension may have an impact on the correlation between SII and FEV1/FVC(p for interaction>0.05). Race may have an effect on the correlation between SII and FVC (p for interaction>0.05). Gender, education level, income level, and BMI may have an impact on the correlation between SII and PEF(p for interaction>0.05). Overall, our study shows a significant negative association between SII and measures of lung function across stratified populations, even after adjusting for multiple confounding factors.
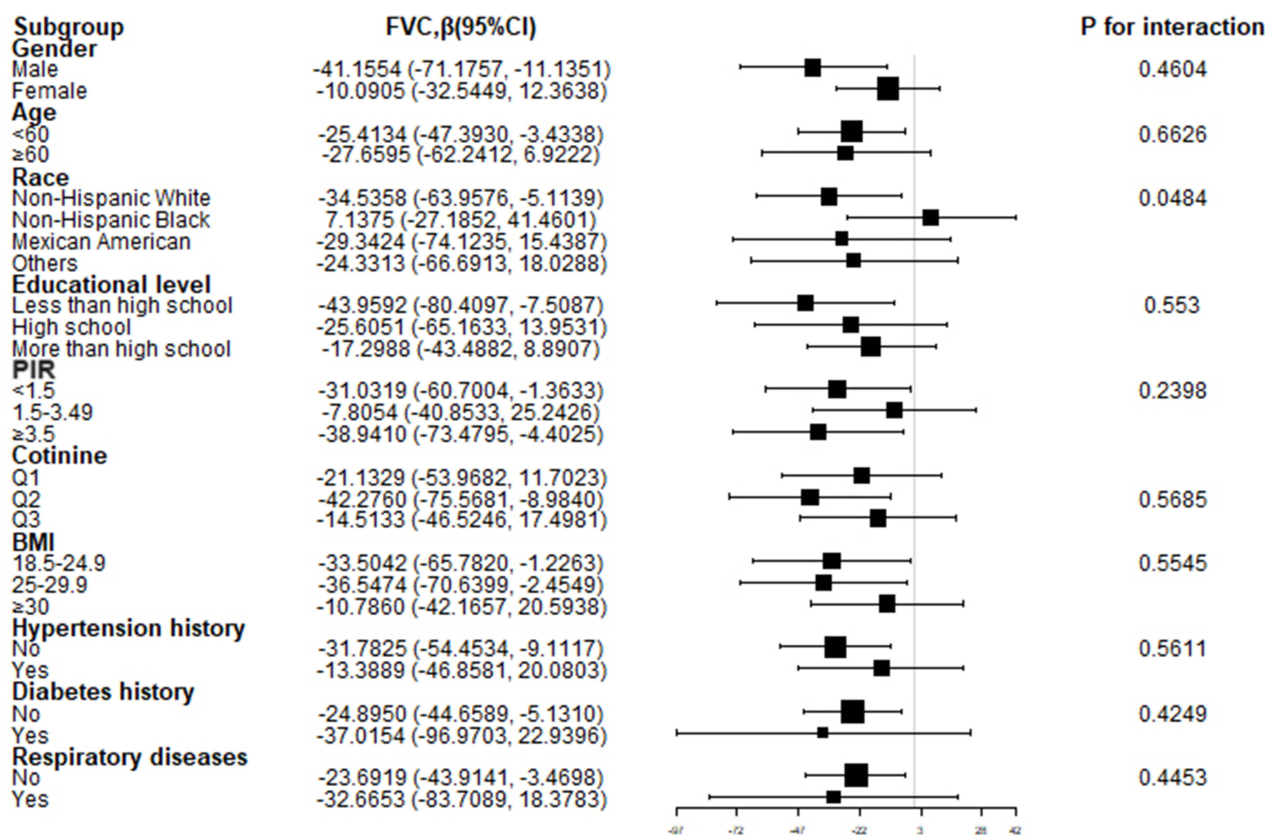
Figure 2 Subgroup analysis of the association between SII and FVC.
Note: Full adjusted for sex, age, race, BMI, education, PIR, cotinine, diabetes, hypertension, and Respiratory diseases.

The Nonlinear Association Between SII and Lung Function

To more clearly present the nonlinear relationship between SII and lung function, the generalized additive model was used to perform smooth curve fitting, and the threshold effect of SII on lung function indicators was further analyzed by two piecewise linear regression models.

As shown in Figure 7, FVC, FEV1, FEV1%, and PEF all showed an inverted U-shaped relationship with Log2-SII. However, there was a negative linear correlation between FEV1/FVC and Log2-SII. Detailed results of the threshold effect analysis are shown in Table 4. In the table, we compare the standard linear model with the two-piecewise linear model. In this study, we found that P = 0.052 for the log-likelihood ratio test between FEV1/FVC and Log2-SII, which means that Model 1(A straight-line effect) should be adopted for this model. There was a negative linear correlation between FEV1/FVC and Log2-SII. However, the P values of the log-likelihood ratio test between Log2-SII and FVC, FEV1, FEV1%, and PEF were all less than 0.05, indicating that a two-piecewise linear regression model should be used to describe the piecewise effects between Log2-SII and FVC, FEV1, FEV1%, PEF. By binary linear regression model and recursive algorithm, cut-off values of the nonlinear relationship between FVC, FEV1, FEV1%, PEF, and Log2-SII were 8.3736, 8.0688, 8.3745, 8.5255, respectively, which were close to 8.5, also suggesting the stability of our results. SII was positively correlated with lung function on the left side of the inflection point and negatively correlated with lung function on the right side of the inflection point; all effect sizes β were statistically significant ($p<0.05$). These results suggest a threshold effect of SII on lung function parameters. Results of all statistical analyses were fully adjusted for confounders.
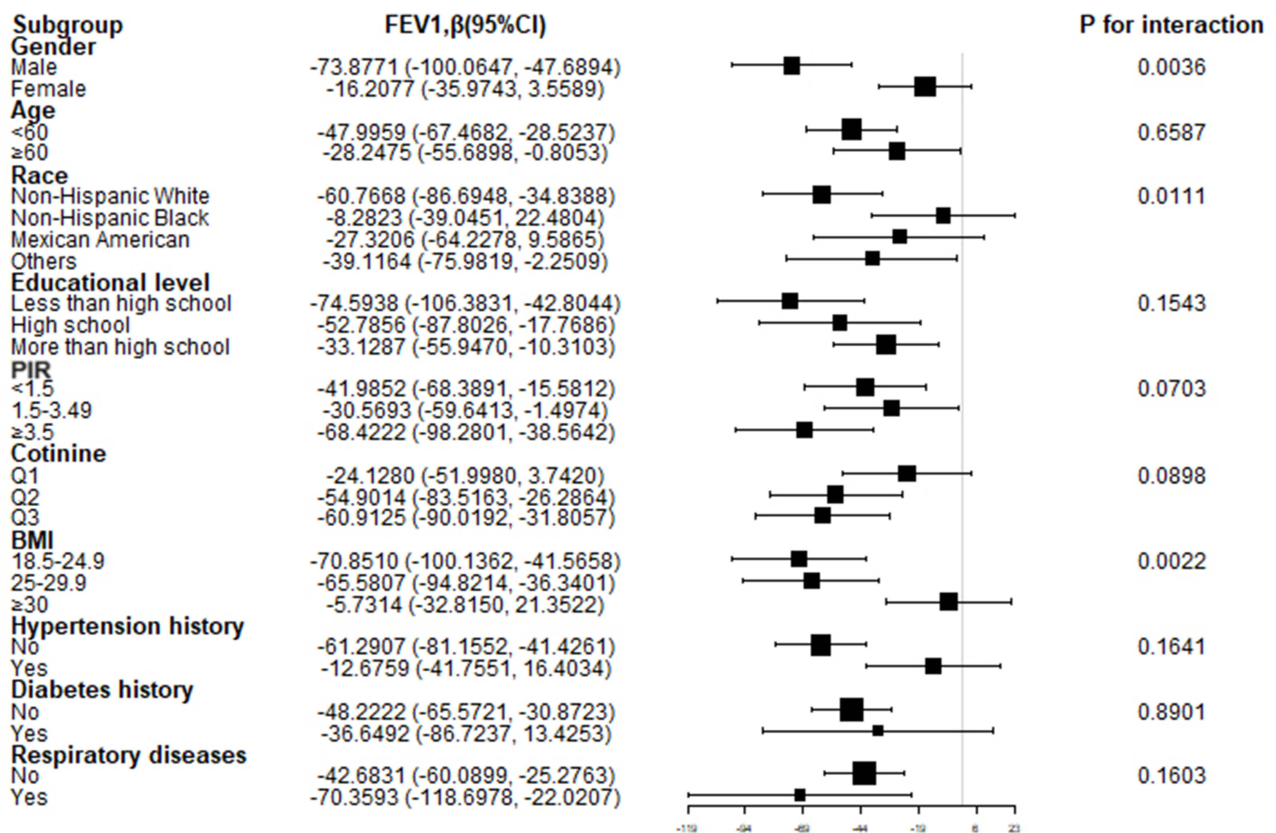
Figure 3 Subgroup analysis of the association between SII and FEV1.
Note: Full adjusted for sex, age, race, BMI, education, PIR, cotinine, diabetes, hypertension, and Respiratory diseases.

Discussion

To the best of our knowledge, the present study is the first to comprehensively explore the relationship between SII and pulmonary function parameters in a large cohort of US adults. This study used NHANES data for three cycles from 2007 to 2012 and included a total of 10,125 American participants aged 18 years and older. This study found significant negative correlations between SII and pulmonary function parameters such as FVC, FEV1, FEV1/FVC, FEV1%, and PEF, after full adjustment for confounding factors. To verify the accuracy and stability of this association, we performed a stratified analysis. The results showed that SII was negatively correlated with pulmonary function indexes in all subgroups except for non-Hispanic blacks in FVC analysis, people with more than high school education in FEV1 analysis, and people with BMI≥30 in FEV1/FVC analysis. We further carried out the smooth curve model and threshold effect analysis, and our study found that, based on the fully adjusted model, there was a linear negative correlation between FEV1/FVC and Log2 SII, while there were clear inverted U-shaped relationships between FVC, FEV1, FEV1%, PEF and Log2 SII. Our study found that the Log2-SII threshold range at which pulmonary function indicators begin to decline is close to 8–8.5. Lung function is an important indicator of lung health, and the decline of lung function often forewarns the occurrence and development of chronic respiratory diseases. The decreased lung function may be related to systemic immune and inflammatory states. Our data suggest that SII is a risk factor for decreased lung function. SII may be an accessible and cost-effective strategy for identifying declines in lung function. This study provides a possible new method for monitoring pulmonary function changes in patients with clinical contraindications.

A large number of studies[30,31] have confirmed that persistent chronic airway inflammation could lead to airway remodeling and small airway obstruction, resulting in decreased lung function. Studies[32] have shown that blocking IL-4R, a common receptor of IL-4 and IL-13, can improve lung function by improving airway inflammation, airway remodeling, and other effects. The mechanism by which WBC negatively correlates with lung function involves the
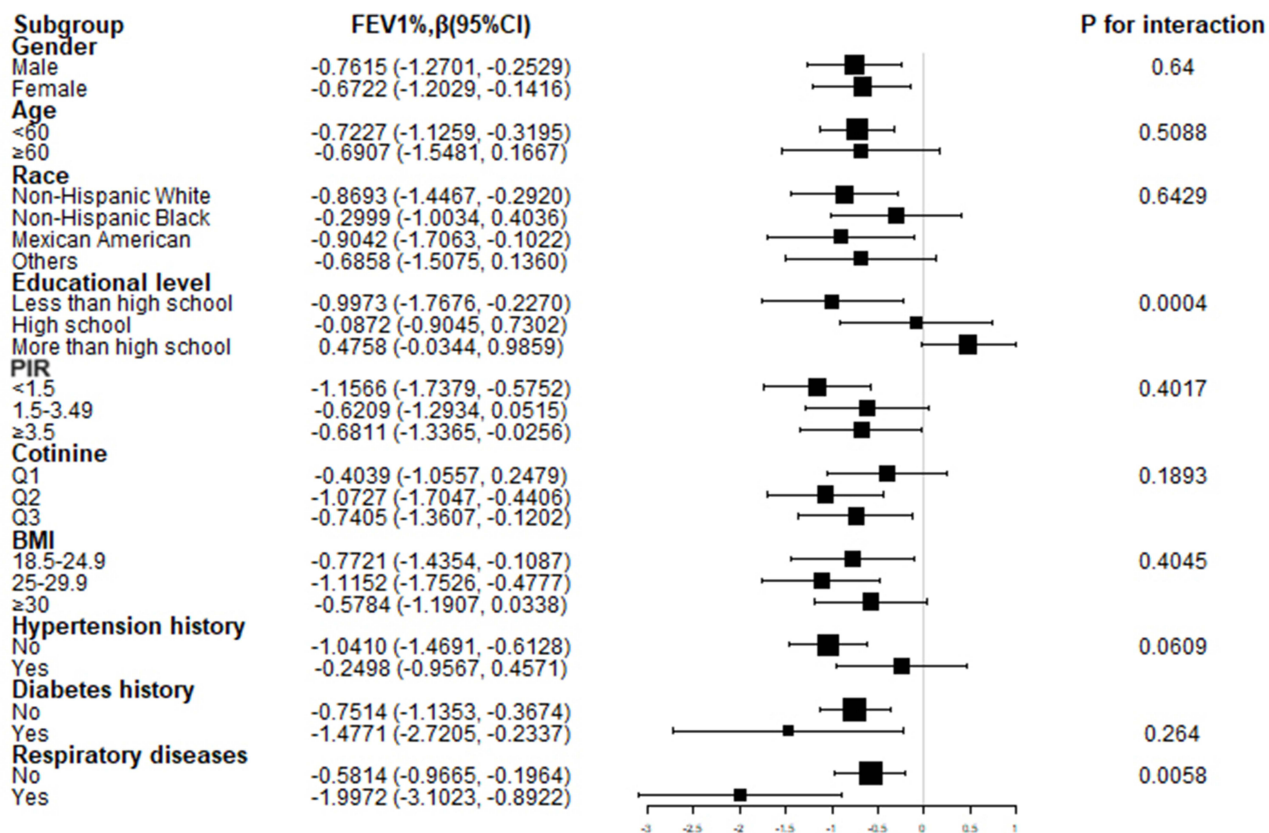
Subgroup	FEV1%, β(95%CI)		P for interaction
Gender			
Male	-0.7615 (-1.2701, -0.2529)		0.64
Female	-0.6722 (-1.2029, -0.1416)		
Age			
<60	-0.7227 (-1.1259, -0.3195)		0.5088
≥60	-0.6907 (-1.5481, 0.1667)		
Race			
Non-Hispanic White	-0.8693 (-1.4467, -0.2920)		0.6429
Non-Hispanic Black	-0.2999 (-1.0034, 0.4036)		
Mexican American	-0.9042 (-1.7063, -0.1022)		
Others	-0.6858 (-1.5075, 0.1360)		
Educational level			
Less than high school	-0.9973 (-1.7676, -0.2270)		0.0004
High school	-0.0872 (-0.9045, 0.7302)		
More than high school	0.4758 (-0.0344, 0.9859)		
PIR			
<1.5	-1.1566 (-1.7379, -0.5752)		0.4017
1.5-3.49	-0.6209 (-1.2934, 0.0515)		
≥3.5	-0.6811 (-1.3365, -0.0256)		
Cotinine			
Q1	-0.4039 (-1.0557, 0.2479)		0.1893
Q2	-1.0727 (-1.7047, -0.4406)		
Q3	-0.7405 (-1.3607, -0.1202)		
BMI			
18.5-24.9	-0.7721 (-1.4354, -0.1087)		0.4045
25-29.9	-1.1152 (-1.7526, -0.4777)		
≥30	-0.5784 (-1.1907, 0.0338)		
Hypertension history			
No	-1.0410 (-1.4691, -0.6128)		0.0609
Yes	-0.2498 (-0.9567, 0.4571)		
Diabetes history			
No	-0.7514 (-1.1353, -0.3674)		
Yes	-1.4771 (-2.7205, -0.2337)		0.264
Respiratory diseases			
No	-0.5814 (-0.9665, -0.1964)		0.0058
Yes	-1.9972 (-3.1023, -0.8922)		

Figure 4 Subgroup analysis of the association between SII and FEV1%.
Note: Full adjusted for sex, age, race, BMI, education, PIR, cotinine, diabetes, hypertension, and Respiratory diseases.

release of proteases by inflammatory cells.[33] Elevated blood neutrophils and monocytes are associated with enhanced innate host defense during bacterial infection. Neutrophils secrete a variety of proteases under the stimulation of pathogenic microorganisms or environmental pollutants. These include serine proteases, such as neutrophil elastase and matrix metalloproteinases, such as MMP-1 and MMP-12, and cysteine proteases (including cathepsin G). Cigarette smoke can cause direct damage to the lung, and it has been reported that smokers have higher neutrophil, monocyte, and eosinophil counts than nonsmokers,[34,35] which will accelerate the decline in lung function in smokers. Omega-3 fatty acids have anti-inflammatory effects, and a large US population study found higher circulating levels were associated with a slower rate of decline in lung function.[11] Inflammation is closely related to impaired lung function. A large number of previous studies have studied the mechanism of single inflammatory cells or inflammatory factors in the occurrence and development of chronic respiratory diseases from the perspective of basic experiments. At present, there is no large-scale population cohort to explore the relationship between comprehensive inflammatory indicators and lung function from the epidemiological perspective and try to determine whether serum comprehensive inflammatory indicators have predictive effects on lung function decline.

SII is a new immune inflammatory indicator that has received more attention in recent years, which was first reported by Hu et al[13] in 2014. Because it can be analyzed using readily available data in blood routine examinations, it is economical and convenient and can be popularized on a large scale. It is based on PLR and NLR, combined with neutrophils, platelets, and lymphocytes, which can more accurately describe the inflammatory and immune status of patients than a single inflammatory indicator. In recent years, the application field of SII has been expanding, and it is widely used in the research of the progression, prognosis, and treatment effect monitoring of cancer and other diseases. Xie et al[36] found an association between SII and the occurrence of cirrhosis. He et al[37] showed that SII was associated with all-cause mortality and poor prognosis in the US population with arteriosclerotic cardiovascular disease (ASCVD).
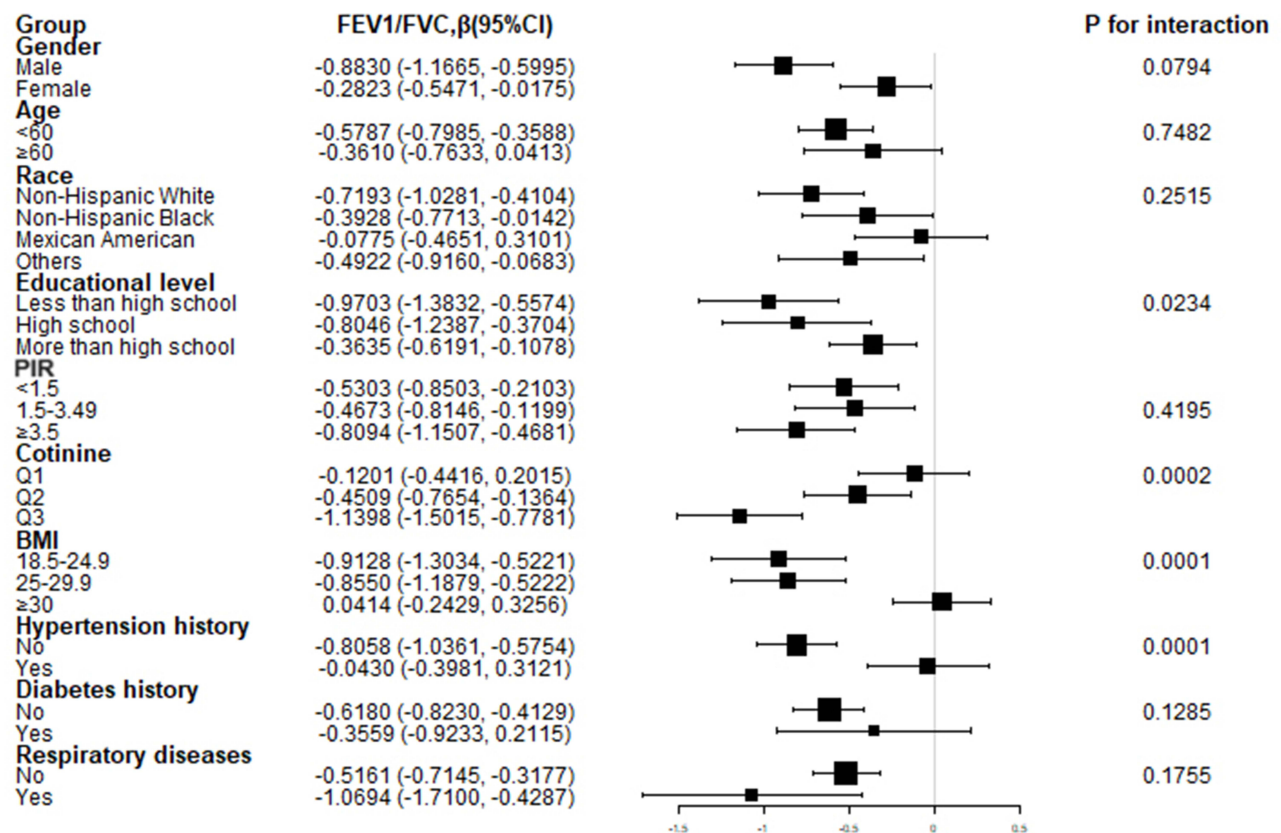
Figure 5 Subgroup analysis of the association between SII and FEV1/FVC.
Note: Full adjusted for sex, age, race, BMI, education, PIR, cotinine, diabetes, hypertension, and Respiratory diseases.

SII is also used in lung diseases, which can be used to evaluate the level of inflammation in patients. At present, it is widely used in clinical research on the prognosis of patients with lung cancer after surgery.[38] SII has shown excellent predictive ability in various studies. At the same time, SII is a generally available method, which is more stable as an easily available comprehensive indicator than blood cell count alone, and is not susceptible to various factors such as dehydration and fluid overload.[39] SII has a good clinical application prospect. At present, there are no large-scale exploratory studies on the relationship between SII and various indicators of lung function.

Firstly, our study found that SII had a very significant negative correlation with various indicators of lung function, even after adjusting for multiple confounding factors such as age, gender, race, BMI, personal history, and history of chronic diseases. Moreover, the trend of progressive decline in lung function with increasing SII was still stable in the trend test and stratified analysis. Studies have shown that T lymphocytes are increased in the lung parenchyma and airways of smokers compared with never smokers, regardless of whether they develop COPD. Compared with CD4+ cells, CD8+ cells increased significantly and also expressed nuclear factor κB (NFκB), signal transducer and activator of transcription 4 (STAT-4), interferon-γ (IFN-γ), and other inflammatory mediators.[40] In addition, T cells can cause lung tissue destruction either directly through cytotoxicity induced by T cells or indirectly through the activation of macrophages.[41] Neutrophils are recruited to the airways of COPD patients and secrete a variety of serine proteases, including neutrophil elastase (NE), matrix metalloproteinase (MMP), and myeloperoxidase (MPO), all of which contribute to alveolar destruction.[42,43] In addition, several neutrophil-derived chemokines, such as IL-1 and CXCL8/IL-8, have been shown to be involved in tissue injury and remodeling in mouse models.[44] The interaction between platelets and inflammatory cells leads to the release of chemokines, which promote the accumulation of immune mediators. Immune mediators are key factors in the formation of atherosclerotic plaques. Studies have shown that platelet activation leads to changes in pulmonary vascular structure and may participate in remodeling of pulmonary artery endothelial structure in various forms,[45] thus leading to lung
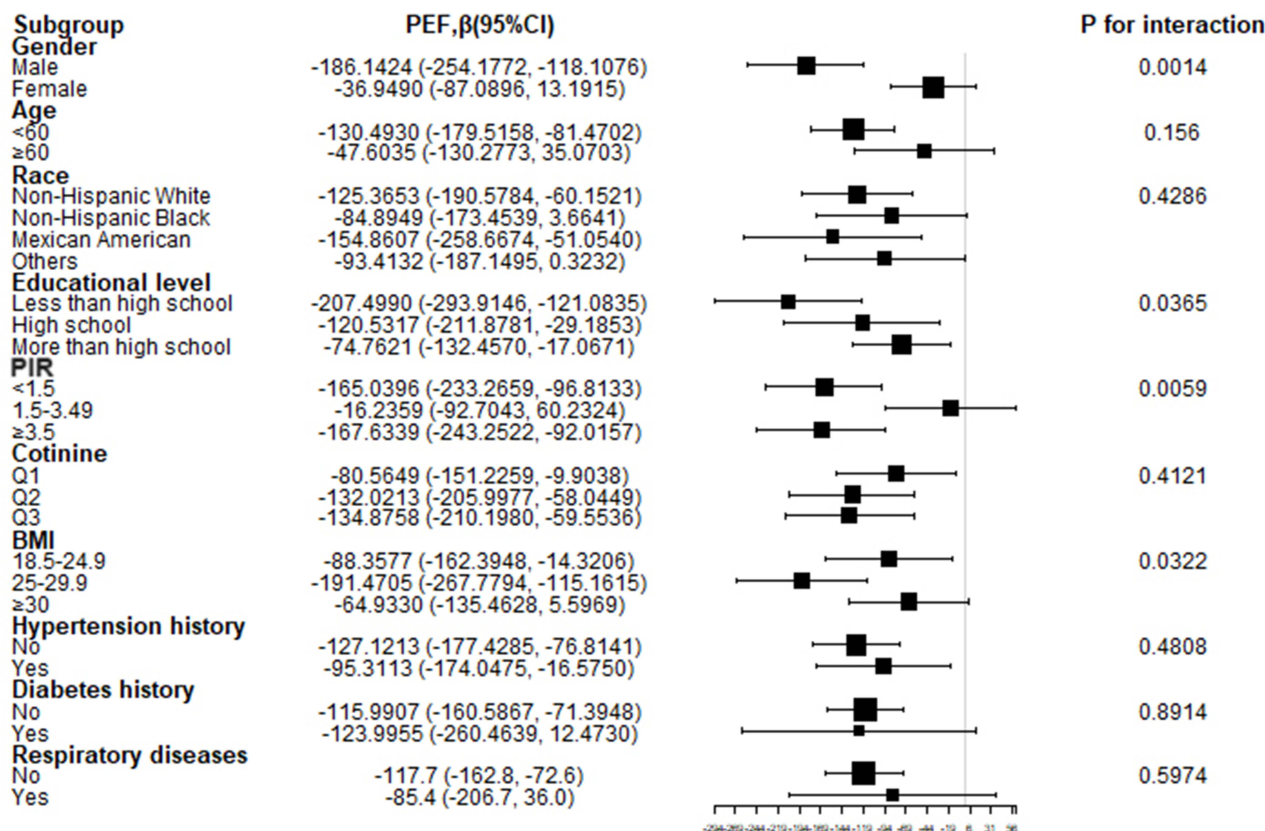
Subgroup	PEF,β(95%CI)		P for interaction
Gender			
Male	-186.1424 (-254.1772, -118.1076)		0.0014
Female	-36.9490 (-87.0896, 13.1915)		
Age			
<60	-130.4930 (-179.5158, -81.4702)		0.156
≥60	-47.6035 (-130.2773, 35.0703)		
Race			
Non-Hispanic White	-125.3653 (-190.5784, -60.1521)		0.4286
Non-Hispanic Black	-84.8949 (-173.4539, 3.6641)		
Mexican American	-154.8607 (-258.6674, -51.0540)		
Others	-93.4132 (-187.1495, 0.3232)		
Educational level			
Less than high school	-207.4990 (-293.9146, -121.0835)		0.0365
High school	-120.5317 (-211.8781, -29.1853)		
More than high school	-74.7621 (-132.4570, -17.0671)		
PIR			
<1.5	-165.0396 (-233.2659, -96.8133)		0.0059
1.5-3.49	-16.2359 (-92.7043, 60.2324)		
≥3.5	-167.6339 (-243.2522, -92.0157)		
Cotinine			
Q1	-80.5649 (-151.2259, -9.9038)		0.4121
Q2	-132.0213 (-205.9977, -58.0449)		
Q3	-134.8758 (-210.1980, -59.5536)		
BMI			
18.5-24.9	-88.3577 (-162.3948, -14.3206)		0.0322
25-29.9	-191.4705 (-267.7794, -115.1615)		
≥30	-64.9330 (-135.4628, 5.5969)		
Hypertension history			
No	-127.1213 (-177.4285, -76.8141)		0.4808
Yes	-95.3113 (-174.0475, -16.5750)		
Diabetes history			
No	-115.9907 (-160.5867, -71.3948)		0.8914
Yes	-123.9955 (-260.4639, 12.4730)		
Respiratory diseases			
No	-117.7 (-162.8, -72.6)		0.5974
Yes	-85.4 (-206.7, 36.0)		

Figure 6 Subgroup analysis of the association between SII and PEF.
Note: Full adjusted for sex, age, race, BMI, education, PIR, cotinine, diabetes, hypertension, and Respiratory diseases.

tissue ischemia and hypoxia. These mechanistic findings may be the potential theoretical basis for the relationship between SII and lung function decline.

Our study has some strengths. This study is the first to investigate the relationship between systemic immune inflammation index and FVC, FEV1, FEV1/FVC, FEV1PRE, PEF, and other lung function indicators based on the NHANES database. Our study was characterized by a large sample size and comprehensive analysis measures. In addition, we adjusted the influence of multiple confounding factors by using weighted linear regression model analysis and carried out sensitivity analysis and comprehensive stratification analysis to make the conclusions of this study more accurate and reliable. Finally, we used smooth curve fitting and threshold effect analysis to find the inverted U-shaped relationship between SII and lung function indicators, and further calculated inflection points that have some predictive value for early detection of lung function decline. The main findings of this study can provide valuable references for clinical practice and future research on lung function protection.

This study also has some limitations. First, because this study is based on a large population survey of NHANES, the causal relationship between SII and lung function cannot be determined, and large-scale prospective validation is needed in the future. Second, the results are limited by the fact that this study was a cross-sectional study design and cannot provide dynamic data on various measures of lung function. Last, due to the lack of data on the use of inhaled medications, such as glucocorticoids, and the severity of symptoms, our results may have been affected by these confounding factors. However, this study provides scientific data reference for future scientific research and clinical practice.
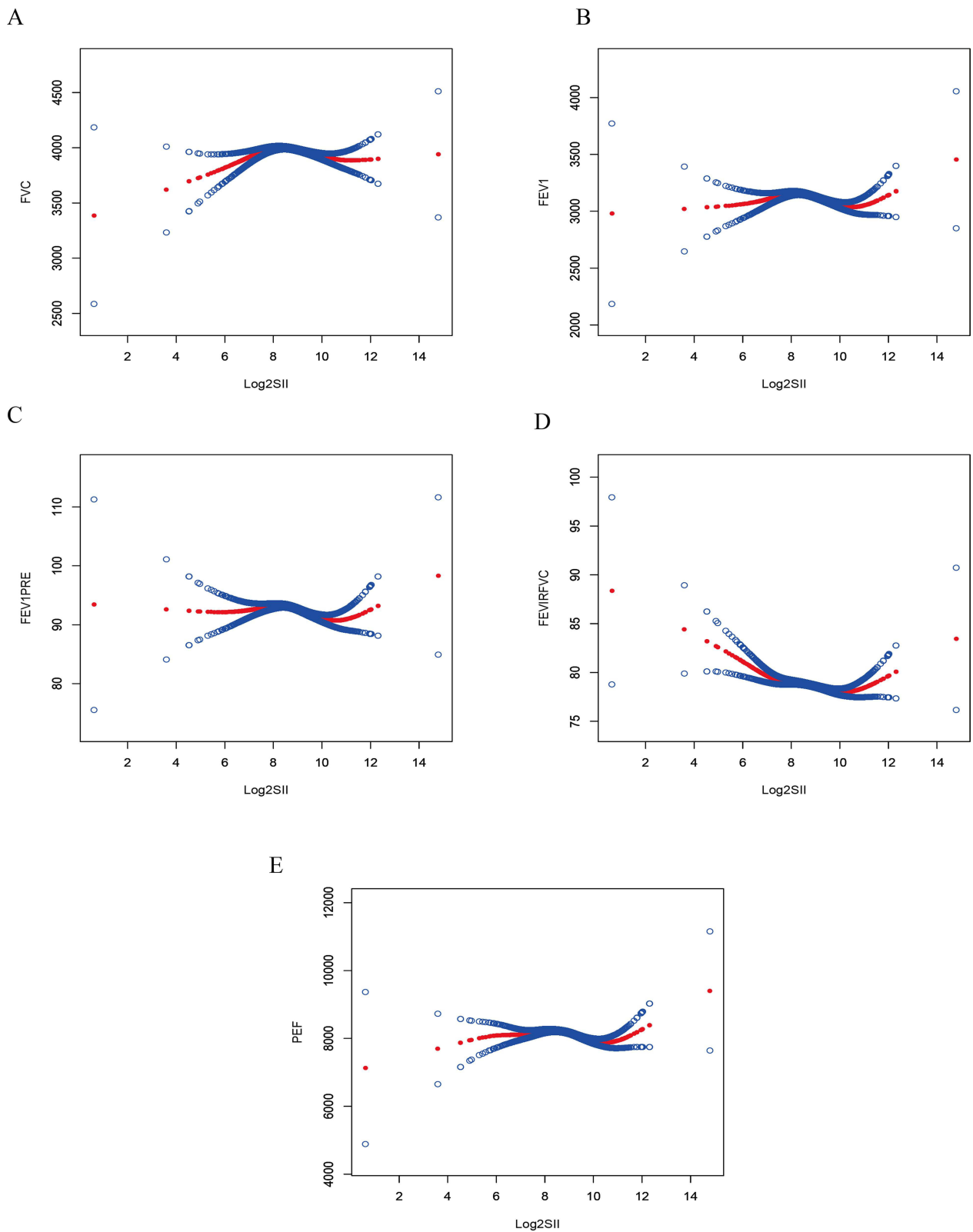
Figure 7 Smooth curve fitting of SII and Pulmonary function.
Notes: Full adjusted for sex, age, race, BMI, education, PIR, cotinine, diabetes, hypertension, and Respiratory diseases. (**A**) SII and FVC; (**B**) SII and FEV1; (**C**) SII and FEV1%; (**D**) SII and FEV1/FVC; (**E**) SII and PEF. FEV1PRE: FEV1 predicted (FEV1%). PEF: peak expiratory flow. The red line in the middle is the fitted line. The blue lines on both sides are the 95% confidence intervals.

Table 4 Analysis of threshold effect and saturation effect about SII on PF

	FVC β(95%CI) *P*-value	FEV1 β(95%CI) *P*-value	FEV1% β(95%CI) *P*-value	FEV1/FVC β(95%CI) *P*-value	PEF β(95%CI) *P*-value
Model I					
A straight-line effect	-26.0994 (-44.9070,-7.2917) 0.0065	-47.4492 (-63.9131,-30.9852) <0.0001	-0.7988 (-1.1656, -0.4319) <0.0001	-0.5932 (-0.7869,-0.3994) <0.0001	-115.2778 (-157.6889,-72.8667) <0.0001
Model II					
Fold points (K)	8.3736	8.0688	8.3745	10.0488	8.5255
Log2-SII< K	97.4850 (44.7059,150.2641) 0.0003	100.8654 (39.2368,162.4940) 0.0013	1.3568 (0.3280, 2.3857) 0.0098	-0.6815 (-0.8947,-0.4683) <0.0001	141.2706 (37.6055,244.9357) 0.0076
Log2-SII>K	-69.0555 (-94.4884,-43.6227) <0.0001	-74.7620 (-94.5124,-55.0116) <0.0001	-1.5494 (-2.0458, -1.0530) <0.0001	0.6165 (-0.6191, 1.8521) 0.3281	-237.6923 (-299.5971,-175.7876) <0.0001
Log likelihood ratio	<0.001	<0.001	<0.001	0.052	<0.001

Notes: Full adjusted for sex, age, race, BMI, education, PIR, cotinine, diabetes, hypertension, and Respiratory diseases. When Log likelihood ratio >0.05, the model showed a Straight-line effect in Model I. When Log likelihood ratio < 0.05, the model showed a segmented effect in Model II. The K value is the inflection point value, which is the level of Log2-SII at which the relationship between SII and lung function changes.

Conclusion

Based on large-scale population studies, we found that SII was significantly negatively correlated with FVC, FEV1, FEV1pre, and PEF, while SII was significantly linearly correlated with FEV1/FVC, and the negative correlation trend remained stable in trend test and stratified analysis. This study determined the SII threshold when lung function indicators began to decline in the overall population. SII may become a promising serological indicator for predicting lung function decline. However, prospective studies were needed to further determine the causal relationship between lung function and SII.

Abbreviations

BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEV1% (FEV1PRE), percent-predicted FEV1; PEF, peak expiratory flow; COPD, chronic obstructive pulmonary disease; SII, systemic immune-inflammation index; PIR, poverty income ratio.

Data Sharing Statement

Data and material are available on reasonable request from corresponding author.

Ethics Approval and Consent to Participate

The portion of this study involving human participants, human material, or human data was conducted in accordance with the Declaration of Helsinki and was approved by the NCHS Ethics Review Committee. All participants provided written informed consent to participate in this study.

This study was based on publicly available data, which was approved by the ethics committee of the Nan Jing Gaochun People's Hospital. No potentially identifiable human images or data are presented in this study.

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Disclosure

The authors report no conflicts of interest in this work.

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