International Journal of Chronic Obstructive Pulmonary Disease

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ORIGINAL RESEARCH

Potential of the Advanced Lung Cancer Inflammation Index as a Risk Marker for Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome and COPD: Evidence from NHANES 2007-2018

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Background: The Advanced Lung Cancer Inflammation Index (ALI) is widely recognized as an emerging metric for assessing both inflammation and nutritional levels. However, it is unclear whether there is a correlation between ALI and Asthma-Chronic Obstructive Pulmonary Disease Overlap (ACO), Chronic Obstructive Pulmonary Disease (COPD), and asthma.

Materials and Methods: ALI was considered as a continuous and categorical variable (Q1, Q2, Q3, Q4), respectively, and the categories of its categorical variables were based on the quartiles of ALI. Logistic regression models were then developed to analyze the correlation between ALI and ACO, COPD, and asthma. Finally, correlations were further analyzed by propensity score matching (PSM) methods. In addition, we calculated the area under the curve (AUC) of the ROC curve to assess the predictive performance of the ALI.

Results: Results with ALI as a continuous variable: ALI was negatively associated with both ACO and COPD (ACO: OR=0.70; 95% CI: 0.58–0.86; $P<0.001$; COPD: OR=0.72; 95% CI: 0.65–0.79; $P<0.001$), whereas there was no association between ALI and asthma (OR=1.08; 95% CI: 0.97–1.20; $P=0.140$). Results of ALI as a categorical variable: the negative ALI-ACO association persisted in Q4 groups (Q4: OR=0.66; 95% CI: 0.49–0.88; $P=0.006$); the negative ALI-COPD association was maintained in all groups. After PSM, ALI remained negatively associated with ACO and COPD (ACO: OR=0.61; 95% CI: 0.45–0.83; $P=0.002$; COPD: OR=0.56; 95% CI: 0.48–0.64; $P<0.001$). The AUC was 0.69 for ALI-ACO and 0.73 for ALI-COPD.

Conclusion: High levels of ALI may be associated with a reduced risk of ACO and COPD.

Keywords: asthma-COPD overlap syndrome, asthma, COPD, nutrient, inflammation

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are common chronic respiratory diseases, mostly characterized by an inflammatory response, with clinical features such as airflow limitation airway remodeling, and airway hyperresponsiveness, respectively, and their mortality and morbidity rates are among the highest in the world.[1–3] Differences exist between asthma and COPD, but patients with features of both asthma and COPD are clinically common, implying that the two can coexist in patients. As a result, the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) have jointly proposed a new disease concept, the asthma-COPD overlap syndrome (ACO). It is defined as a disease characterized by both asthma and COPD.[4] In the 2021 GOLD report, the word ACO is recommended to be discontinued, and they place more emphasis on the fact that asthma

Received: 20 January 2025
Accepted: 24 March 2025
Published: 31 March 2025

and COPD are differentiated and are distinct diseases.[2] However, healthcare professionals continue to have extensive discussions about the ACO in the clinical frontline.

The advanced lung cancer inflammation index (ALI) is a comprehensive index that combines the level of inflammation and nutritional status. It integrates body mass index, albumin, and neutrophil-to-lymphocyte ratio (NLR) for comprehensive assessment, and it is widely used in the assessment of the survival prognosis of lung cancer patients.[5] Some studies have previously shown that low levels of ALI can reflect high levels of inflammation and poorer nutrition.[6,7] Given that disease progression is the result of multiple factors, a single consideration of the impact of inflammation levels on a patient's prognosis may be insufficient, and therefore the ALI may be of more value and potential for clinical guidance than a single indicator of inflammation. Chronic respiratory diseases are known to have an inherently inflammatory response, while respiratory muscle mass and strength are closely related to nutritional status. It is well known that chronic respiratory diseases are inherently characterized by an inflammatory response, while respiratory muscle mass and strength are closely related to nutritional status.[8] Therefore, the use of the ALI to assess ACO, COPD, and asthma is in the fundamental interest of patients. One study has shown that the lower the body mass index, the faster the decline in lung function is likely to be.[9] This seems to prove that a single assessment of inflammation is not optimal for patients with respiratory disease. There is clinical value in exploring the potential correlation between ALI and ACO, COPD, and asthma through the present study.

Materials and Methods

Data Sources

The data for this study came from the National Health and Nutrition Examination Survey (NHANES), which utilizes multistage stratified sampling to examine the health of the US population and was also approved by the National Center for Health Statistics (NCHS) Research Ethics Board. Initially, data information on 59,842 participants was obtained from publicly available data from 2007 through 2018 through a search of NHANES data. Subsequently, participants whose data were missing or unavailable for adjudication among the independent and dependent variables were excluded, and data from 21,123 participants were finally included, and the detailed screening can be seen in Figure 1. It is worth noting that the NHANES database provides weighting information to make the data nationally representative, and the 2-year sample weights (wtmec2yr) were also used in this study. More details can be found at the following link: https://www.cdc.gov/nchs/nhanes/index.htm.

Calculation of ALI

Chronic diseases of the respiratory system are highly susceptible to body weight, nutritional status, and inflammation levels, so we used the ALI to comprehensively assess the impact on risk for ACO, COPD, and asthma. The ALI is

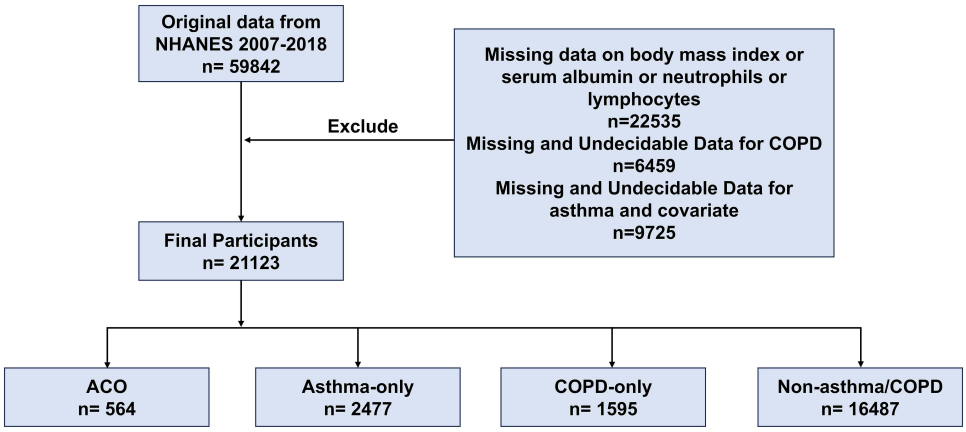

Figure 1 Flowchart of the sample selection from NHANES 2007–2018.
Abbreviations: NHANES, National Health and Nutrition Examination Survey; ACO, Asthma-Chronic Obstructive Pulmonary Disease overlap; COPD, Chronic Obstructive Pulmonary Disease.

calculated using the following formula: BMI (kg/m2)×serum albumin level (g/dL)/neutrophil-to-lymphocyte ratio (NLR). In this study, due to the skewed distribution of ALI, it was logarithmically processed before analysis. Participants will then be categorized into four groups based on the quartiles of the ALI, from smallest to largest Quantile1 group (Q1), Quantile2 group (Q2), Quantile3 group (Q3), and Quantile4 group (Q4). A trend test was also performed to analyze whether the trend of change between the four groups was statistically different ($P<0.05$).

Outcome

The current study categorized participants into four categories: 1. non-COPD/asthma participants; 2. COPD-only participants; 3. asthma-only participants; and 4. ACO participants. The diagnosis of participants with COPD relied on a standardized medical status questionnaire administered during the interview and a pulmonary function test: 1. Participants were asked "Have you been told by a healthcare professional that you have COPD" and were diagnosed with COPD if they answered yes;2. The ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) (FEV1/FVC) was less than 0.70 after inhalation of bronchodilators. The diagnosis of asthma was determined using a standardized questionnaire: 1. Whether or not the person had ever been told they had asthma, and if the answer was yes, the diagnosis was asthma. The diagnosis of ACO patients, on the other hand, is dependent on COPD and asthma, which are manifested by fulfilling the diagnostic requirements for both COPD and asthma. In the current study, participants with COPD and asthma only were defined as COPD patients and asthma patients.

Covariates

In this study, the effects of various covariates were considered. Based on clinical observations and other studies, the following covariates were included in this study: age, gender, race, education, family poverty income ratio (PIR), marital status, high blood pressure, diabetes, smoking, drinking, and cancer.[10,11] Age, gender, race, education, marital status, and household income poverty ratios are from the Demographic Statistics module. Age was categorized into four groups based on interval segments (20 to 39 years, 40 to 59 years, and 60 to 80 years). Educational levels were categorized into three groups based on educational status (Above high school degree, high school degree, and less than high school degree). PIR was categorized into low-income (<1), middle-income (≥1,<4), and high-income (≥4) based on the ratio. The diagnosis of high blood pressure (HBP), diabetes, cancer, and alcohol consumption relied on the questionnaire portion of the questionnaire, which was ultimately categorized into two groups (diseased and non-diseased). Smoking status, on the other hand, was categorized into current smokers, past smokers, and non-smokers depending on how well participants responded to two specific questions. Participants were first asked if they had smoked more than 100 cigarettes in their lifetime, and if they answered yes, they were defined as smokers, and vice versa as non-smokers; smokers were then continued to be asked, do you smoke now, and if they answered yes, they were positioned as current smokers, and vice versa as past smokers.

Statistical Analyses

The weights provided by NHANES (wtmec2yr) were used in this study to meet the basic requirements of multi-stage stratified sampling so that the data could be representative and to generalize the results of the analysis to the whole country. All variables were transformed into categorical variables and expressed as quantities (percentages). The current study used a weighted logistic regression model to analyze the correlation between ALI and ACO, COPD, and asthma. There are three models based on the inclusion of covariates: model 1 does not correct for the effects of covariates on the regression model; model 2 corrects for the effects of age, gender, and race covariates on the regression model; and model 3 corrects for the effects of all covariates on the regression model.

In this study, restricted cubic spline (RCS) plots were used to analyze whether there was a potential nonlinear relationship between ALI and disease. Subgroup analyses were also conducted to explore the correlation between ALI and disease in different contexts such as age, gender, education, marital status, and household income poverty ratio. Also, the p-value for the interaction of ALI with each covariate was obtained by comparing the main effect and interaction term regression models. Finally, to further improve the reliability of the associations, the current study conducted a PSM analysis by pairing the disease and non-disease groups of ACO and COPD in 1:1 pairs. In addition, the present study

conducted Receiver Operating Characteristic (ROC) curve test to explore the predictive performance of the model. The analysis of this study was performed using R 4.4.1 and $P < 0.05$ was considered statistically different.

Results

Characteristics of the Population

A total of 21,123 participants were included in this study, of which 10,469 were male and 10,654 were female, a ratio of approximately 1 to 1. The smallest number of participants were included in the 60 to 80 age group, with similar percentages in the 20 to 39 and 40 to 59 age groups. The largest percentage of participants with asthma disease was between the ages of 20 and 39 years (47.44%), which may suggest that asthma is characterized by a younger age group. The largest proportion of participants with COPD were between 60 and 80 years of age (42.55%), suggesting that the elderly population should be a priority for COPD prevention. ACO participants were similarly represented among 40 to 59-year-olds and 60 to 80-year-olds and were much higher than among 20 to 39-year-olds. Participants with higher education (Above high school degree) were much higher than those with other education in any subgroup. More detailed baseline characteristics can be found in Table 1.

Regression Analysis results

Details of the ALI correlation results with ACO, COPD, and asthma can be seen in Table 2. The results showed that ALI exhibited negative correlations with ACO and COPD in all three models: model 1 (ACO: OR=0.59; 95% CI: 0.49–0.73; $P<0.001$; COPD: OR=0.56; 95% CI: 0.51–0.62; $P<0.001$), model 2 (ACO: OR=0.64; 95% CI: 0.53–0.78, $P<0.001$; COPD: OR=0.65; 95% CI: 0.59–0.71; $P<0.001$), model 3 (ACO: OR=0.70; 95% CI: 0.58–0.86; $P<0.001$; COPD: OR=0.72; 95% CI: 0.65–0.79; $P<0.001$). ALI and asthma found no evidence of a correlation in all three models ($P>0.05$).

Sensitivity analyses were subsequently performed with the following results: in the ALI-ACO model 1 without correction for covariates, higher ALI levels and lower ACO risk were statistically significant ($P<0.05$); In Model 2, only participants in the Q2 and Q4 groups maintained a negative correlation between ALI and ACO compared to the Q1 reference group (Q2: OR=0.74, 95% CI: 0.55–0.99, $P=0.042$; Q4: OR=0.60, 95% CI: 0.46–0.79, $P<0.001$); In Model 3, participants in the Q4 group may have had a 34% lower risk of ACO (OR: 0.66, 95% CI: 0.49–0.88, $P=0.006$). ACO may reduce risk with increasing ALI levels (P for trend ≤ 0.014). Participants in the Q2, Q3 and Q4 groups showed a negative correlation between ALI and COPD in ALI-COPD models 1, 2, and 3. Reduced risk of COPD may be associated with elevated ALI levels (P for trend < 0.001).

Restricted Cubic Spline Plots

There was no nonlinear relationship between ALI and ACO and COPD, and high levels of ALI were associated with low risk of ACO and COPD, as detailed in Figure 2A and B.

Subgroup Analysis

Detailed results of the ALI-ACO subgroup analysis can be seen in Figure 3A. The negative ALI-ACO association remained except among participants aged 20 to 39 weeks, diabetic participants, cancer participants, non-smoking participants, and non-drinkers. In addition, gender, HBP, and alcohol consumption interacted with ALI (P for interaction < 0.05).

Detailed results of the ALI-COPD subgroup analyses are shown in Figure 3B. The correlations remained negative except for participants aged 20 to 39 years and non-drinkers. ALI interacted with gender and smoking (P for interaction < 0.05).

Propensity Score Matching Analysis

Because of the large difference between participants in the disease and non-disease groups, PSM analyses were considered in the current study to further analyze the correlation. A total of 1122 participants were included in the ALI-ACO correlation analysis, with a 50/50 split between ACO and non-ACO participants, and a total of 4282 participants were included in the ALI-COPD correlation analysis, with a 50/50 split between COPD and non-COPD participants. The

Table 1 Table of Baseline Population Characteristics (Weighted)

Characteristic	Overall N = 147,536,099	Non-asthma/COPD N = 114,044,4931	Asthma-only N = 18,137,345	COPD-only N = 11,406,730	ACO N = 3,947,532	p-value
Age						<0.001
20–39 years	55,161,812.85 (37.39%)	43,406,769.19 (38.06%)	8,604,713.81 (47.44%)	2,127,203.30 (18.65%)	1,023,126.55 (25.92%)	
40–59 years	57,042,617.63 (38.66%)	45,285,743.08 (39.71%)	5,850,286.29 (32.26%)	4,425,923.52 (38.80%)	1,480,664.73 (37.51%)	
60–80 years	35,331,668.62 (23.95%)	25,351,980.60 (22.23%)	3,682,344.84 (20.30%)	4,853,602.80 (42.55%)	1,443,740.38 (36.57%)	
Gender						<0.001
Male	72,914,714.75 (49.42%)	57,107,978.21 (50.08%)	7,216,206.24 (39.79%)	6,761,914.15 (59.28%)	1,828,616.15 (46.32%)	
Female	74,621,384.35 (50.58%)	56,936,514.67 (49.92%)	10,921,138.70 (60.21%)	4,644,815.47 (40.72%)	2,118,915.52 (53.68%)	
Race						<0.001
Mexican American	12,676,913.17 (8.59%)	10,990,056.76 (9.64%)	1,024,427.52 (5.65%)	538,948.96 (4.72%)	123,479.92 (3.13%)	
Other Hispanic	8,316,479.85 (5.64%)	6,860,333.98 (6.02%)	1,048,931.13 (5.78%)	256,129.02 (2.25%)	151,085.73 (3.83%)	
Non-Hispanic White	100,459,351.33 (68.09%)	75,649,511.03 (66.33%)	12,527,867.53 (69.07%)	9,219,706.94 (80.83%)	3,062,265.83 (77.57%)	
Non-Hispanic Black	15,511,397.10 (10.51%)	12,129,148.51 (10.64%)	2,243,596.74 (12.37%)	745,645.36 (6.54%)	393,006.49 (9.96%)	
Other/multiracial	10,571,957.65 (7.17%)	8,415,442.60 (7.38%)	1,292,522.02 (7.13%)	646,299.34 (5.67%)	217,693.69 (5.51%)	
Education						<0.001
Above high school degree	92,534,944.79 (62.72%)	72,043,809.87 (63.17%)	12,023,300.48 (66.29%)	6,242,962.63 (54.73%)	2,224,871.81 (56.36%)	
High school degree	32,218,309.16 (21.84%)	24,609,523.99 (21.58%)	3,694,184.24 (20.37%)	2,950,976.85 (25.87%)	963,624.09 (24.41%)	
Less than high school	22,782,845.15 (15.44%)	17,391,159.02 (15.25%)	2,419,860.22 (13.34%)	2,212,790.14 (19.40%)	759,035.77 (19.23%)	
Marital status						<0.001
cohabitation	94,862,607.97 (64.30%)	74,059,578.35 (64.94%)	10,504,235.17 (57.91%)	7,967,891.86 (69.85%)	2,330,902.59 (59.05%)	
solitary	52,673,491.13 (35.70%)	39,984,914.52 (35.06%)	7,633,109.77 (42.09%)	3,438,837.76 (30.15%)	1,616,629.08 (40.95%)	
PIR						0.003
High income	52,155,512.94 (35.35%)	40,774,222.95 (35.75%)	6,238,657.16 (34.40%)	3,939,310.21 (34.53%)	1,203,322.62 (30.48%)	
Low income	19,524,439.77 (13.23%)	14,332,652.28 (12.57%)	2,936,944.62 (16.19%)	1,486,875.89 (13.04%)	767,966.97 (19.45%)	
Middle income	75,856,146.39 (51.42%)	58,937,617.65 (51.68%)	8,961,743.15 (49.41%)	5,980,543.52 (52.43%)	1,976,242.07 (50.06%)	
HBP						<0.001
HBP	45,164,739.53 (30.61%)	33,152,706.45 (29.07%)	5,936,754.96 (32.73%)	4,385,072.96 (38.44%)	1,690,205.16 (42.82%)	
Non-HBP	102,371,359.57 (69.39%)	80,891,786.43 (70.93%)	12,200,589.98 (67.27%)	7,021,656.65 (61.56%)	2,257,326.51 (57.18%)	
Diabetes						<0.001
Diabetes	14,095,584.67 (9.55%)	10,241,234.23 (8.98%)	1,975,175.67 (10.89%)	1,333,822.34 (11.69%)	545,352.44 (13.82%)	
Non-diabetes	133,440,514.43 (90.45%)	103,803,258.65 (91.02%)	16,162,169.27 (89.11%)	10,072,907.28 (88.31%)	3,402,179.23 (86.18%)	
Cancer						<0.001
Cancer	14,052,790.07 (9.52%)	9,636,254.20 (8.45%)	1,845,017.10 (10.17%)	1,862,092.49 (16.32%)	709,426.29 (17.97%)	
Non-cancer	133,483,309.03 (90.48%)	104,408,238.68 (91.55%)	16,292,327.84 (89.83%)	9,544,637.13 (83.68%)	3,238,105.38 (82.03%)	
Smoke						<0.001
Smoker	29,754,213.08 (20.17%)	20,161,199.82 (17.68%)	3,914,517.96 (21.58%)	4,338,861.36 (38.04%)	1,339,633.93 (33.94%)	
Former smoker	35,966,033.30 (24.38%)	26,647,943.91 (23.37%)	4,155,866.17 (22.91%)	3,780,371.29 (33.14%)	1,381,851.93 (35.01%)	
Non-smoker	81,815,852.73 (55.45%)	67,235,349.15 (58.96%)	10,066,960.81 (55.50%)	3,287,496.97 (28.82%)	1,226,045.80 (31.06%)	
Drink						<0.001
Drinker	115,562,674.99 (78.33%)	88,439,169.30 (77.55%)	14,214,195.82 (78.37%)	9,610,123.86 (84.25%)	3,299,186.01 (83.58%)	
Non-drinker	31,973,424.11 (21.67%)	25,605,323.57 (22.45%)	3,923,149.12 (21.63%)	1,796,605.76 (15.75%)	648,345.65 (16.42%)	

Notes: All values in the baseline table are weighted; N-Weighted sample size.

Abbreviations: ACO, Asthma-Chronic Obstructive Pulmonary Disease overlap; COPD, Chronic Obstructive Pulmonary Disease; PIR,family poverty income ratio; HBP, high blood pressure.

https://doi.org/10.2147/COPD.S518600

Table 2 Results of the Correlation of ALI with ACO, COPD and Asthma (Weighted)

ACO	Model1		Model2		Model3	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Continuous	0.59(0.49,0.73)	<0.001	0.64(0.53,0.78)	<0.001	0.70(0.58,0.86)	<0.001
COPD	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Continuous	0.56(0.51,0.62)	<0.001	0.65(0.59,0.71)	<0.001	0.72(0.65,0.79)	<0.001
Asthma	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Continuous	1.06(0.96, 1.18)	0.200	1.07(0.97,1.18)	0.200	1.08(0.97,1.20)	0.140
ACO	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Categories						
Q1	reference		reference		reference	
Q2	0.70(0.52,0.94)	0.020	0.74(0.55,0.99)	0.042	0.78(0.58,1.04)	0.090
Q3	0.74(0.58,0.92)	0.009	0.80(0.64,1.01)	0.059	0.87(0.68,1.11)	0.300
Q4	0.55(0.41,0.72)	<0.001	0.60(0.46,0.79)	<0.001	0.66(0.49,0.88)	0.006
P for trend		<0.001		0.001		0.014
COPD	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Categories						
Q1	reference		reference		reference	
Q2	0.70(0.60,0.82)	<0.001	0.76(0.65,0.89)	<0.001	0.80(0.69,0.94)	0.008
Q3	0.65(0.57,0.75)	<0.001	0.73(0.64,0.85)	<0.001	0.81(0.70,0.95)	0.009
Q4	0.50(0.44,0.57)	<0.001	0.59(0.52,0.68)	<0.001	0.67(0.57,0.77)	<0.001
P for trend		<0.001		<0.001		<0.001

Notes: Q1, Q2, Q3 and Q4 are groupings after quartile classification; model 1-No adjustment for covariates; model 2-Adjustment for age, gender and race covariates; model 3-Fully adjusted covariates.
Abbreviations: ALI, advanced lung cancer inflammation index; ACO, Asthma-Chronic Obstructive Pulmonary Disease overlap; COPD, Chronic Obstructive Pulmonary Disease; OR, Odd Ratio; CI, confidence interval.

number of participants included was small, and to visualize the participants, an unweighted number was used for the baseline characteristics table after PSM; more details can be found in Table 3. After PSM, ALI as a continuous variable remained negatively associated with ACO and COPD (ACO: OR=0.61; 95% CI: 0.45–0.83; *P*=0.002; COPD: OR=0.56;

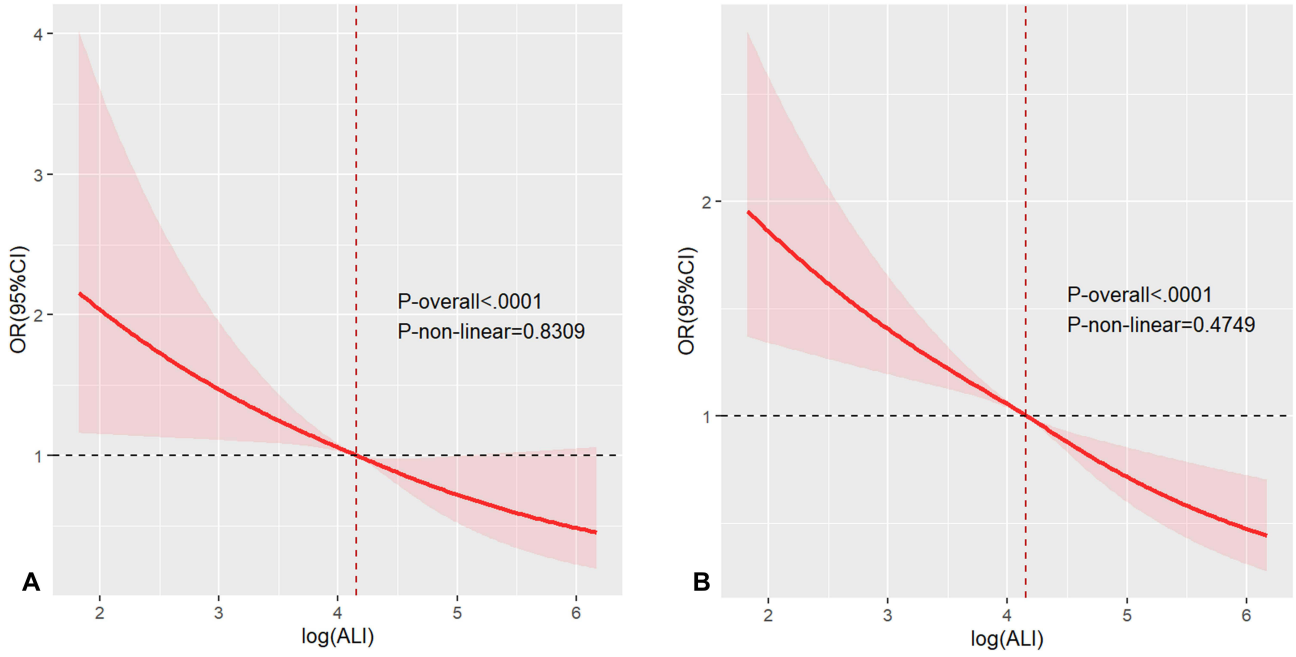

Figure 2 Restricted cubic spline plots for ALI-ACO and ALI-COPD. **(A)**: Restricted cubic spline plots for ALI-ACO; **(B)**: Restricted cubic spline plot for ALI-COPD.
Abbreviations: ALI, advanced lung cancer inflammation index; ACO, Asthma-Chronic Obstructive Pulmonary Disease overlap; COPD, Chronic Obstructive Pulmonary Disease.

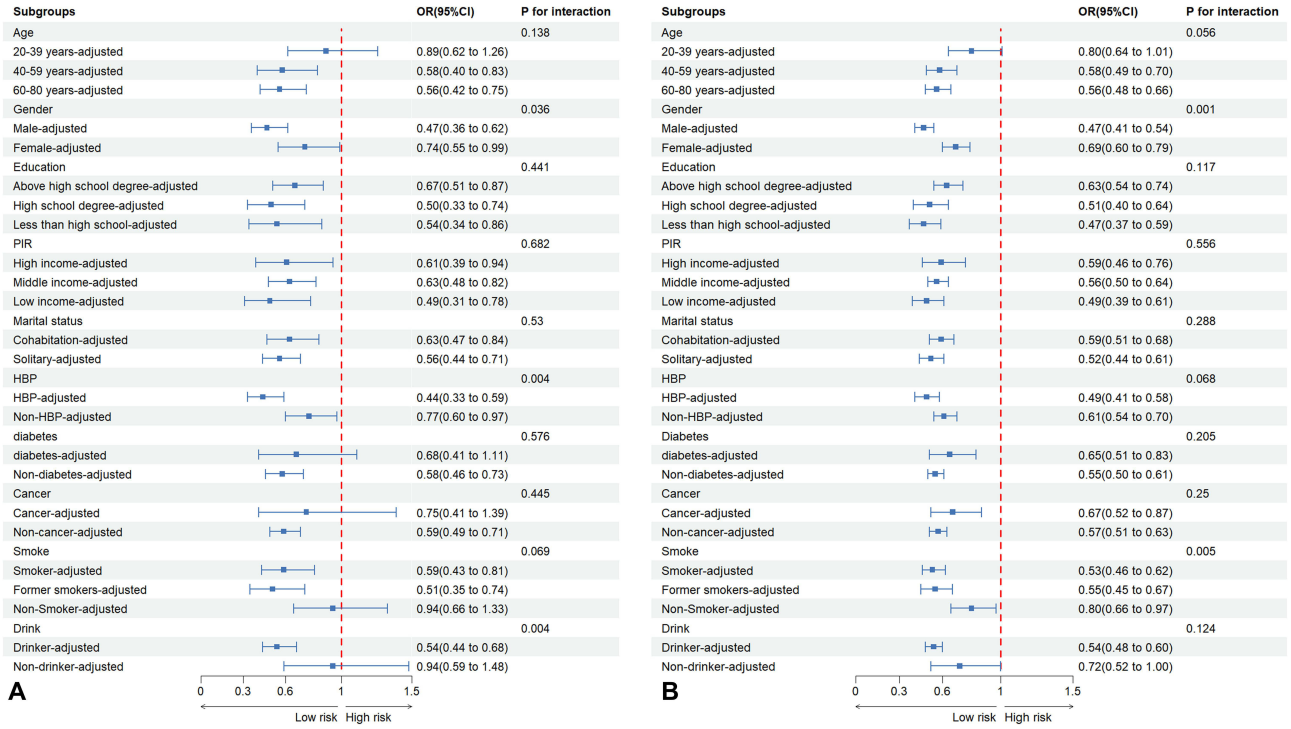

Figure 3 Forest plot results of subgroup analysis of ALI-ACO and ALI-COPD. **(A)**: Forest plot results of subgroup analysis of ALI-ACO; **(B)**: Forest plot results of subgroup analysis of ALI-COPD.

Abbreviations: ALI, advanced lung cancer inflammation index; ACO, Asthma-Chronic Obstructive Pulmonary Disease overlap; COPD, Chronic Obstructive Pulmonary Disease; PIR, family poverty income ratio; HBP, high blood pressure.

95% CI: 0.48–0.64; $P<0.001$). The negative association of ALI as a categorical variable with COPD remained in every group; with ACO, the negative ALI-ACO association was maintained only in the Q4 group (Q4: OR=0.53; 95% CI: 0.43–0.65; $P<0.001$). In addition, the trend test for ALI as a categorical variable versus ACO in the analysis of model 1 was not significant ($P=0.057$), which implies that the results of this model 1 are unreliable, and more details can be found in Table 4.

Table 3 Baseline Characteristics of the Population After PSM Analysis

Characteristic	Overall n = 1,122	Non-ACO n = 561	ACO n = 561	p-value	Overall n = 4,282	Non-COPD n = 2141	COPD n = 2,141	p-value
Age				0.8				0.6
20–39 years	310.00 (25.57%)	155.00 (25.35%)	155.00 (25.82%)		901.00 (21.09%)	455.00 (21.43%)	446.00 (20.72%)	
40–59 years	348.00 (36.73%)	168.00 (35.84%)	180.00 (37.69%)		1,331.00 (37.80%)	665.00 (36.81%)	666.00 (38.85%)	
60–80 years	464.00 (37.70%)	238.00 (38.81%)	226.00 (36.49%)		2,050.00 (41.12%)	1,021.00 (41.76%)	1,029.00 (40.44%)	
Gender				0.8				0.8
Male	544.00 (46.89%)	275.00 (47.28%)	269.00 (46.46%)		2,493.00 (55.26%)	1,242.00 (55.01%)	1,251.00 (55.52%)	
Female	578.00 (53.11%)	286.00 (52.72%)	292.00 (53.54%)		1,789.00 (44.74%)	899.00 (44.99%)	890.00 (44.48%)	
Race				0.9				0.2
Mexican American	74.00 (3.19%)	37.00 (3.23%)	37.00 (3.14%)		429.00 (4.48%)	220.00 (4.59%)	209.00 (4.36%)	
Non-Hispanic Black	249.00 (9.84%)	127.00 (9.69%)	122.00 (10.00%)		763.00 (7.52%)	385.00 (7.55%)	378.00 (7.49%)	
Non-Hispanic White	642.00 (78.28%)	325.00 (79.03%)	317.00 (77.46%)		2,532.00 (80.66%)	1,256.00 (81.47%)	1,276.00 (79.79%)	
Other Hispanic	76.00 (3.34%)	32.00 (2.87%)	44.00 (3.85%)		276.00 (2.63%)	131.00 (2.58%)	145.00 (2.68%)	
Other/multiracial	81.00 (5.35%)	40.00 (5.17%)	41.00 (5.54%)		282.00 (4.72%)	149.00 (3.81%)	133.00 (5.68%)	
Education				0.7				>0.9
Above high school degree	568.00 (57.66%)	289.00 (58.77%)	279.00 (56.46%)		2,014.00 (55.72%)	1,014.00 (55.94%)	1,000.00 (55.48%)	
High school degree	271.00 (24.10%)	134.00 (23.78%)	137.00 (24.44%)		1,063.00 (25.44%)	519.00 (25.39%)	544.00 (25.50%)	
Less than high school	283.00 (18.24%)	138.00 (17.45%)	145.00 (19.10%)		1,205.00 (18.84%)	608.00 (18.67%)	597.00 (19.02%)	

(*Continued*)

https://doi.org/10.2147/COPD.S518600

Table 3 (Continued).

Characteristic	Overall n = 1,122	Non-ACO n = 561	ACO n = 561	p-value	Overall n = 4,282	Non-COPD n = 2141	COPD n = 2,141	p-value
Marital status				0.4				0.7
cohabitation	582.00 (57.90%)	290.00 (56.57%)	292.00 (59.34%)		2,622.00 (67.13%)	1,318.00 (67.45%)	1,304.00 (66.79%)	
solitary	540.00 (42.10%)	271.00 (43.43%)	269.00 (40.66%)		1,660.00 (32.87%)	823.00 (32.55%)	837.00 (33.21%)	
PIR				>0.9				0.6
High income	236.00 (30.60%)	121.00 (30.56%)	115.00 (30.63%)		932.00 (33.50%)	464.00 (33.20%)	468.00 (33.82%)	
Low income	311.00 (18.99%)	153.00 (18.93%)	158.00 (19.06%)		905.00 (13.68%)	444.00 (13.09%)	461.00 (14.31%)	
Middle income	575.00 (50.41%)	287.00 (50.51%)	288.00 (50.31%)		2,445.00 (52.82%)	1,233.00 (53.71%)	1,212.00 (51.87%)	
HBP				0.8				0.9
HBP	531.00 (43.18%)	265.00 (43.77%)	266.00 (42.53%)		1,839.00 (39.25%)	912.00 (39.12%)	927.00 (39.38%)	
Non-HBP	591.00 (56.82%)	296.00 (56.23%)	295.00 (57.47%)		2,443.00 (60.75%)	1,229.00 (60.88%)	1,214.00 (60.62%)	
Diabetes				0.9				0.3
Diabetes	192.00 (13.57%)	91.00 (13.75%)	101.00 (13.39%)		615.00 (11.68%)	288.00 (11.06%)	327.00 (12.33%)	
Non-diabetes	930.00 (86.43%)	470.00 (86.25%)	460.00 (86.61%)		3,667.00 (88.32%)	1,853.00 (88.94%)	1,814.00 (87.67%)	
Cancer				0.5				0.8
Cancer	168.00 (16.60%)	83.00 (15.71%)	85.00 (17.57%)		617.00 (16.35%)	300.00 (16.18%)	317.00 (16.53%)	
Non-cancer	954.00 (83.40%)	478.00 (84.29%)	476.00 (82.43%)		3,665.00 (83.65%)	1,841.00 (83.82%)	1,824.00 (83.47%)	
Smoke				0.8				0.7
Smoker	388.00 (32.70%)	192.00 (31.85%)	196.00 (33.61%)		1,596.00 (35.94%)	810.00 (35.51%)	786.00 (36.40%)	
Former smoker	361.00 (36.48%)	180.00 (37.68%)	181.00 (35.18%)		1,373.00 (33.61%)	673.00 (33.33%)	700.00 (33.91%)	
Non-smoker	373.00 (30.82%)	189.00 (30.46%)	184.00 (31.21%)		1,313.00 (30.44%)	658.00 (31.16%)	655.00 (29.68%)	
Drink				0.2				0.14
Drinker	920.00 (84.84%)	467.00 (86.08%)	453.00 (83.49%)		3,491.00 (84.84%)	1,764.00 (85.71%)	1,727.00 (83.92%)	
Non-drinker	202.00 (15.16%)	94.00 (13.92%)	108.00 (16.51%)		791.00 (15.16%)	377.00 (14.29%)	414.00 (16.08%)	

Notes: All values in the baseline table are unweighted; n- Unweighted sample size.
Abbreviations: PSM, Propensity Score Matching; ACO, Asthma-Chronic Obstructive Pulmonary Disease overlap; COPD, Chronic Obstructive Pulmonary Disease; PIR, family poverty income ratio; HBP, high blood pressure.

Table 4 Results of Correlation of ALI with ACO and COPD After PSM Analysis

	Model1		Model2		Model3	
ACO	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Continuous	0.68(0.52,0.89)	0.005	0.63(0.47,0.85)	0.003	0.61(0.45,0.83)	0.002
COPD	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Continuous	0.59(0.51,0.67)	<0.001	0.56(0.49,0.65)	<0.001	0.56(0.48,0.64)	<0.001
ACO	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Categories						
Q1	reference		reference		reference	
Q2	0.80(0.51,1.25)	0.300	0.76(0.49,1.20)	0.200	0.76(0.48,1.20)	0.200
Q3	0.85(0.62,1.16)	0.300	0.82(0.59,1.14)	0.200	0.81(0.58,1.13)	0.200
Q4	0.70(0.50,0.97)	0.034	0.65(0.45,0.94)	0.021	0.63(0.42,0.93)	0.020
P for trend		0.057		0.038		0.029
COPD	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Categories						
Q1	reference		reference		reference	
Q2	0.74(0.60,0.91)	0.004	0.73(0.59,0.89)	0.003	0.73(0.59,0.90)	0.003
Q3	0.71(0.58,0.86)	<0.001	0.69(0.57,0.84)	<0.001	0.68(0.56,0.83)	<0.001
Q4	0.55(0.46,0.67)	<0.001	0.54(0.44,0.65)	<0.001	0.53(0.43,0.65)	<0.001
P for trend		<0.001		<0.001		<0.001

Notes: Q1, Q2, Q3 and Q4 are groupings after quartile classification; model 1-No adjustment for covariates; model 2-Adjustment for age, gender and race covariates; model 3-Fully adjusted covariates.
Abbreviations: ALI, advanced lung cancer inflammation index; ACO, Asthma-Chronic Obstructive Pulmonary Disease overlap; COPD, Chronic Obstructive Pulmonary Disease; PSM, Propensity Score Matching; OR, Odd Ratio; CI, confidence interval.

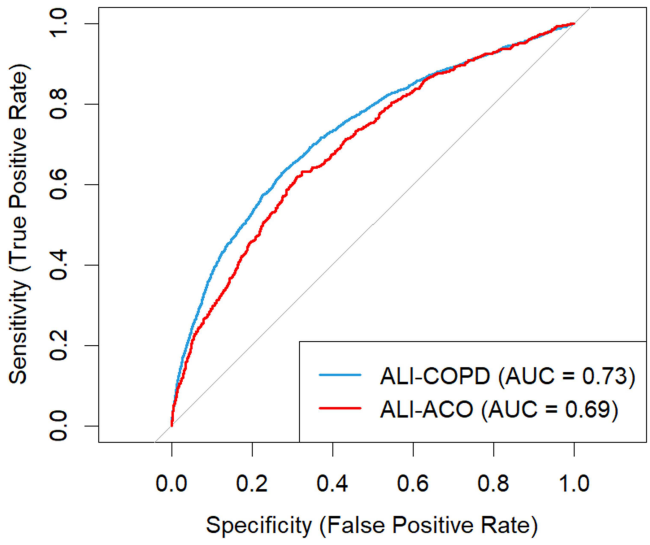

Figure 4 ROC curves for ALI-ACO and ALI-COPD.
Abbreviations: ALI, advanced lung cancer inflammation index; ACO, Asthma-Chronic Obstructive Pulmonary Disease overlap; COPD, Chronic Obstructive Pulmonary Disease; AUC, area under the curve; ROC, Receiver Operating Characteristic.

Predictive Performance of ALI for COPD and ACO Prediction

The ROC curve can display the area under the curve (AUC) to test the predictive ability of ALI for COPD and ACO, as detailed in Figure 4. The results showed that the AUC is 0.73 in the ALI-COPD model and 0.69 in the ALI-ACO model. This suggests that ALI has a higher ability to predict COPD than ACO, and that ALI may have more potential for use in the COPD population.

Discussion

The current study was based on data from a nationally representative sample and found correlation results between ALI and ACO, COPD. The results of the current study showed that after adjusting for all covariates, ALI remained negatively associated with ACO and COPD. In addition, to improve statistical validity and reduce the number of confounders, a PSM analysis was performed, which showed that ALI remained negatively associated with ACO and COPD. This means that higher levels of ALI may be a protective measure for patients with ACO and COPD.

The ALI is a composite index that includes body mass index, serum albumin level, and NLR. The BMI is widely used as an indicator for assessing obesity in humans, which has received greater attention in the respiratory system.[12,13] Obesity itself is also a chronic metabolic disease characterized by increased body fat and is one of the leading causes of fatal illness and death, as well as a potential risk factor for respiratory diseases.[14–16] Excessive obesity may reduce the expression of cilia-related genes, leading to decreased airway mucus cilia clearance, which increases the chance of respiratory infections and is a risk factor for respiratory tract.[17] It also seems possible that excessive obesity directly increases the risk of mechanical restriction of ventilatory function in the organism, which is undoubtedly a major risk for patients with COPD.[18] In addition, although the causes of asthma are complex, obesity exacerbates the risk of asthma and increases airway hyperresponsiveness as confirmed by research.[19–21] It is logical that ACO, as an overlapping sign of asthma and COPD, has a strong association with obesity.

Currently, obesity can be categorized into central and peripheral obesity based on the primary location of fat accumulation. Central obesity is predominantly characterized by abdominal fat accumulation and can be assessed by waist circumference.[22] A cross-sectional study once noted a negative correlation between waist circumference and lung function and emphasized the importance of regulating abdominal obesity for lung function in middle-aged and older Americans.[23] The exact mechanism between the two, although unknown, may be since the accumulation of fat in the abdomen leads to a restriction of respiratory function, which in turn leads to a reduction in the patient's lung capacity and the development of lower tidal volumes, which is also a major detriment to the respiratory system.[24] It may also be due to

 https://doi.org/10.2147/COPD.S518600

reduced respiratory muscle strength due to obesity.[25] Interestingly, most obese patients will have a concurrent loss of muscle mass and function, which is referred to as sarcopenic obesity.[26] Decreased muscle Dnaja3 haploinsufficiency and consequent dysregulation of lipid metabolism may explain this phenomenon.[27] This does not seem to be good news for the respiratory muscle groups of the respiratory system. Obesity also seems to intervene in the inflammatory response, because the accumulation of lipids in fat cells leads to increased levels of inflammation.[28] Thus, from an inflammatory perspective, obesity remains a risk factor for ACO, COPD, and asthma. Controlling obesity and maintaining a good body mass index is undoubtedly good health management, and intervention at an early stage is very likely to improve lung function.[29] Physical exercise is the best way to reduce your fat content. Interestingly, one study noted that physical activity itself also reduces the risk of COPD and asthma.[30]

It is worth noting that one of the causes of excessive obesity may be due to abnormalities in lipid metabolism, usually seen in adipocyte proliferation and deficits in lipid homeostasis.[31] Outside of that, high cholesterol levels raise the risk of oxidation of unsaturated fats, which means that being attacked by reactive oxygen species becomes easier, triggering an inflammatory response.[32] At the same time, dyslipidemia may also usually result from the influence of pro-inflammatory adipokines.[33]

Serum albumin is the predominant protein in the body's plasma and plays a role in maintaining the body's nutritional and osmotic pressures, and higher serum albumin levels are an indicator of good health has been confirmed by research.[34] It has been suggested that body serum albumin levels are closely related to the health status and prognosis of respiratory patients and that maintaining good serum albumin levels is beneficial to patients with respiratory diseases.[35] In addition, the administration of adequate nutritional support is associated with reduced levels of inflammatory response.[36] Interestingly, the onset of inflammation accelerates protein breakdown as well as induces anorexia, which ultimately leads to lower albumin levels and weight loss.[37,38] Reliance on a single inflammatory marker such as interleukin-6 and procalcitonin is no longer sufficient, and an assessment that balances BMI and albumin levels may be more comprehensive.

Inflammation plays a very important role in the development of COPD and asthma.[39,40] NLR has been widely used in inflammation as an easily accessible biomarker.[41] In acute exacerbations of COPD (AECOPD), NLR rises with increasing levels of inflammation. The results of one retrospective study suggest that NLR can be used for prognostic assessment in patients with AECOPD.[42] In the population of asthmatics, the NLR is equally useful for assessment, especially when the diagnosis is not clear or is uncertain from other test results.[43,44] This may result from group 2 innate lymphoid cells (ILC2s) promoting airway inflammation by secreting type 2 cytokines.[45] ILC2s are key mediators of inflammation and play an important role in the development of respiratory inflammation.[46] It has also been noted that interleukin 33 also stimulates ILC2 and rapidly induces airway constriction.[47] This is obviously not a boon to patients with respiratory problems.

In the current study, we found a negative correlation between ALI and ACO, COPD. It is worth noting that when ALI was controlled for as a continuous variable in the correlation analysis with asthma, Models 1, 2, and 3 showed no evidence of correlation. In the subgroup analyses of ALI-ACO, the ALI-ACO association was not maintained among participants aged 20 to 39 years, diabetic participants, cancer participants, non-smoking participants, and non-drinkers; and in the subgroup analyses of ALI-COPD, the ALI-COPD association was not being maintained among participants aged 20 to 39 years and non-drinkers. This may be due to the relatively small sample sizes for the stratification variables.

In conclusion, ALI may have more clinical potential and significance than a single biomarker, and maintaining a high level of ALI may significantly reduce the risk of ACO and COPD. The data for this study came from NHANES, which includes sample data from across the country, making the results reliable and nationally generalizable. Second, to improve the accuracy and stability of the results, we included representative confounders for correction, such as demographic information, smoking, alcohol consumption, and hypertension. Finally, this study further analyzed the association between ALI and disease using PSM analysis, strengthening the reliability of the results.

However, there are also shortcomings in this study. First, for the diagnosis of the disease, we mainly relied on questionnaires, although the diagnosis of COPD also relied on the FEV1/FVC, which could still make the present study potentially biased due to the lack of a clear diagnosis. Second, disease progression is usually the result of a combination

of organismic and multifactorial factors, so there may have been confounding factors that were not included in this study. Third, the components of ALI, BMI, albumin, and NLR, are strongly associated with chronic airway disease and lung function decline, so there is some potential for ALI to be affected by the development of COPD, which implies that there may be a vicious circle.[48] Fourth, this study did not provide data on air pollution exposures and occupational exposures that are closely related to the respiratory system, so the comprehensiveness of the data needs to be taken into account in further future analyses.[49,50] Finally, the current study is a cross-sectional study, and the results are interpreted as correlations rather than as a more definitive causal effect relationship. The results of this study and the underlying mechanisms of their correlation need to be studied and explored further.

Conclusion

ALI may be a new biologic indicator in patients with ACO and COPD as well as high levels of ALI may be associated with a reduced risk of ACO and COPD.

Data Sharing Statement

All statistics from this study can be found in the NHANES database: https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics Approval and Consent to Participate

All study protocols were approved by the Research Ethics Review Board of the National Center for Health Statistics, and all subjects provided written informed consent prior to medical examination. According to the Measures for Ethical Review of Life Science and Medical Research Involving Human Beings (China, February 18, 2023), Article 32, items 1 and 2, ethical review is not required for research using legally obtained publicly available data, data generated by non-invasive observation of public behavior, or anonymized data:https://www.gov.cn/zhengce/zhengceku/2023-02/28/content_5743658.htm.

Acknowledgments

We are very grateful to the participants from NHANES 2007-2018.

Funding

This study was supported by the Project of Science and Technology Development Program of Traditional Chinese Medicine of Shandong Province (2017-117), and the Project of Science and Technology of Traditional Chinese Medicine of Shandong Province (2020M022).

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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