Lipids in Health and Disease

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Systemic inflammation partially mediates the association between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and chronic cough

Changfen Wang[1†], Xuecheng Liao[1†], Jiulin Chen[1], Ying Lan[3] and Jun Wen[2*†]

Abstract

Background Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR), a new biomarker, reflects blood lipid status. Nevertheless, the association between NHHR and chronic cough remains uncertain.

Method This investigation included 9725 individuals from the NHANES. This research employed multiple statistical models to illustrate the association between NHHR and chronic cough. These models included logistic regression models, the Shapley Additive Explanations (SHAP) model, trend tests, mediation analysis, restricted cubic splines (RCS), and subgroup analyses.

Result The logistic regression model, adjusting all covariables, showed a positive association between NHHR with chronic cough (OR: 1.08; 95% CI: 1.02–1.14). Trend tests and RCS further proved that NHHR and chronic cough had a linear and positive association. The mediation analysis proved that systemic immune inflammation index (SII) and systemic inflammatory response index (SIRI) partially mediated the association between NHHR and chronic cough. The SHAP model suggested that the top five important markers for predicting chronic cough were SII, smoking, NHHR, BMI, and SIRI.

Conclusion This investigation discovered that NHHR was positively associated with chronic cough. Regular NHHR monitoring may serve as a potential tool for identifying individuals at higher risk of chronic cough.

Keywords Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR), Chronic cough, Systematic inflammation, Mediation analysis, Shapley additive explanations (SHAP)

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Introduction

Chronic cough is a frequent presentation in respiratory clinics and often signifies underlying respiratory or non-respiratory conditions. While it was previously defined epidemiologically as a cough persisting for more than three months, current clinical guidelines classify it as a cough lasting longer than eight weeks as the primary symptom [1, 2]. A retrospective meta-analysis reported that the prevalence of chronic cough around the world has been estimated to vary from 2 to 18% in diverse geographical regions [3]. If left untreated and unresolved, prolonged coughing can trigger a variety of detrimental effects on both the physical and psychological well-being of individuals, ultimately diminishing quality of life [4–6]. Aside from that, chronic cough is often seen merely as a symptom rather than a standalone clinical condition, it can lessen the diagnosis precision. For this reason, individuals suffering from chronic cough are likely to experience an elevated economic burden, predominantly encompassing direct costs such as medical consultations, medications, diagnosis, and hospitalization, as well as indirect costs including lowered productivity and absenteeism [7–9].

Notwithstanding the paucity of clinical research exploring the link between dyslipidemia and chronic cough, multiple studies have delved into the sophisticated connection between lipid metabolism and inflammatory lung disease. The risk of respiratory conditions may be exacerbated by dyslipidemia through inflammatory responses and oxidative stress [10]. As previously illustrated, variations in lipid metabolism may contribute to the development and advancement of COPD [11]. A 10-year follow-up retrospective cohort study revealed that individuals with hyperlipidemia had a 1.48-fold increased risk of developing COPD compared to those without it [12]. An inverse link between asthma incidence and levels of serum cholesterol as well as non-high-density lipoprotein cholesterol (NHDL-C) was found after serum cholesterol measurements were analyzed in 7,005 participants by Michael et al. Conversely, no statistically significant association was observed between asthma and high-density lipoprotein cholesterol (HDL-C) levels [13]. Nonetheless, a bidirectional two-sample Mendelian randomization study arrived at an utterly dissimilar conclusion that the elevated LDL is casually bound up with cholesterol levels, lowered HDL levels and heightened risk of asthma [14].

The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR), a novel composite index, serves as an effective measure of atherogenic lipid profiles. Previous studies have demonstrated that NHHR outperforms conventional lipid parameters in predicting the risk of cardiovascular disease, insulin resistance, and metabolic syndrome [15–17].

Given its established utility, investigating the relationship between NHHR and chronic cough may offer valuable insights into the interplay between lipid metabolism and lung diseases. Studies have highlighted the potential role of systemic inflammation and metabolic dysregulation in the pathogenesis of chronic cough [9, 18]. Inflammation plays a central role in the pathogenesis of chronic cough, including local airway inflammation, systemic inflammation, and inflammation-mediated cough hypersensitivity [19, 20]. Interestingly, earlier studies have reported an inverse association between NHHR levels and asthma prevalence, while a positive association has been observed with COPD risk. However, the potential link between NHHR and chronic cough remains underexplored. To address this gap, this study utilized data from the National Health and Nutrition Examination Survey (NHANES) to examine the association between NHHR and chronic cough.

Materials and methods

Study population

The purpose of NHANES is to provide policymakers with nutritional and medical information on American adults and children. It is freely available to the public and updated frequently. The data analyzed of the investigation originated from the 2007–2012 NHANES. Exclusion criteria included: [1] those missing chronic cough data; [2] people with either HDL-C or NHDL-C missing; and [3] people with missing covariables. In the end, 9725 individuals were assigned to this investigation. The analyzed populations' screening process diagram was apparent in Fig. 1.

Assessment of NHHR and chronic cough

The University of Minnesota received the prepared and preserved blood samples for examination. Blood HDL-C and total blood cholesterol concentrations were quantified using enzymatic techniques. ***NHHR = (Total cholesterol - HDL-C) / HDL-C.*** This study determined whether the subjects had a chronic or non-chronic cough using the standard questionnaire. A physician or other health care provider asked the participant, "Do you often experience a cough on most days for a duration of three continuous months or longer each year?" When the participant responded "yes," the participant was determined to have a chronic cough.

Covariables

Some covariables were incorporated into the investigation to reduce the potential effect caused by confounding factors. This study included the following confounding factors: sex, race, age, smoking, alcohol, education, marriage, body mass index (BMI), hypertension, diabetes, cardiovascular disorder (CVD), asthma, emphysema,

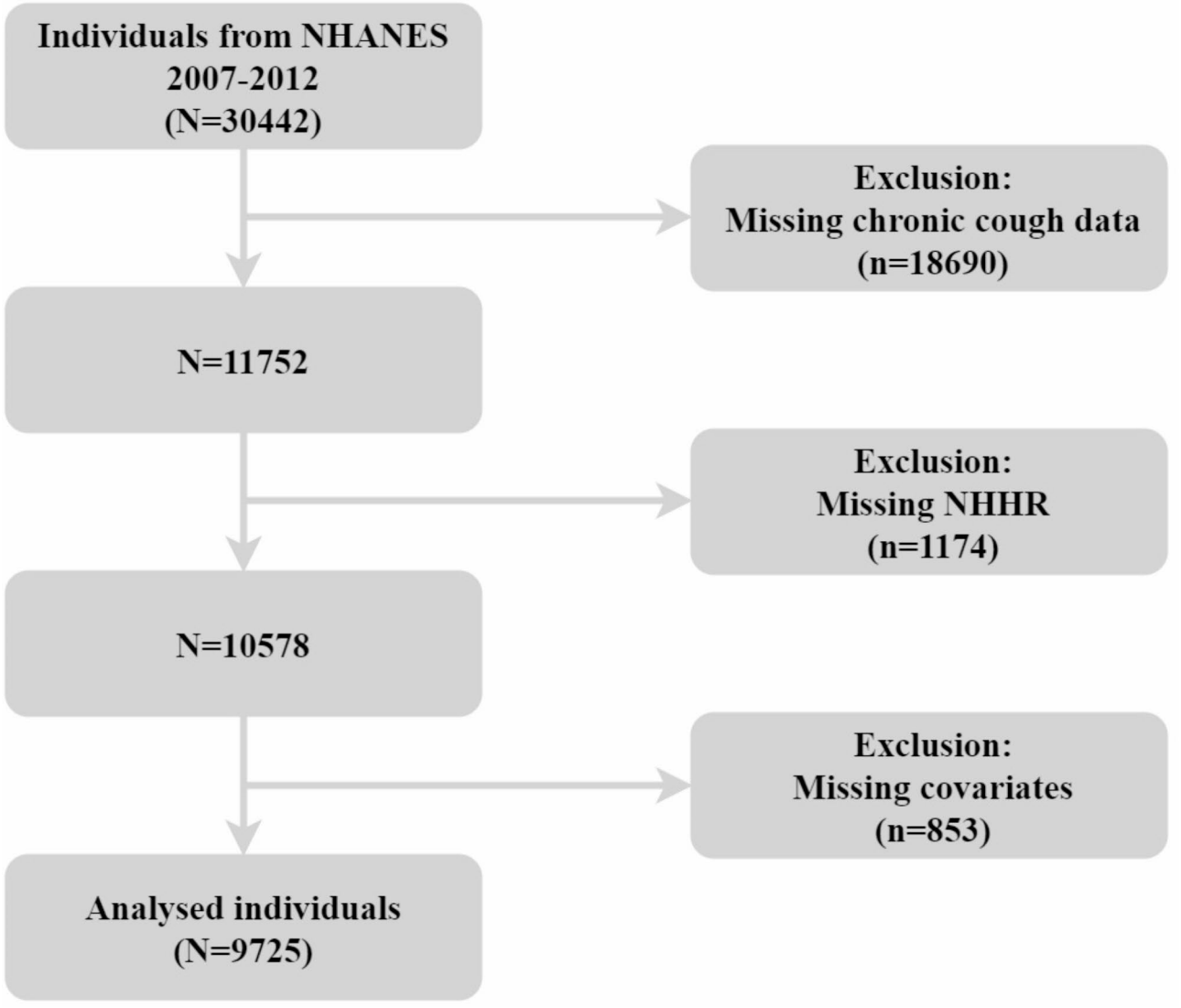

Fig. 1 Screening process diagram for analyzed population

chronic bronchitis, cancer, systemic immune inflammation index (SII = platelet number * neutrophil number/lymphocyte number), and systemic inflammation response index (SIRI = monocyte number * neutrophil number/lymphocyte number) [21].

Statistical analysis

This investigation applied the chi-square test to acquire the *P*-value for categorical data and the Kruskal-Wallis rank-sum test to acquire the *P*-value for continuous data. For non-normally distributed continuous data, this investigation utilized the median and IQR, whereas for those with normal distribution, this investigation employed the mean and SE. Percentages were implemented to describe categorical data. This investigation initially adopted three logistic regression analyses and trend tests to assess the relationship between NHHR and chronic cough. Restrictive cubic splines (RCS), based on logistic regression models, were employed to better quantify the dose-response association between NHHR and chronic cough. Subsequently, this investigation implemented the mediation effect model to assess the contribution of systematic inflammation to the association between NHHR and chronic cough. Afterwards, this study used the SHAP model with XGBoost to determine the importance of each variable identifying associations with chronic cough. Ultimately, this research performed subgroup analyses and sensitivity analyses using data derived from multiple imputations. This survey applied "MICE" package to handle the lack of covariables (education, marriage, BMI, smoking, alcohol, hypertension, diabetes, CVD, asthma, chronic bronchitis, emphysema, cancer, SII, and SIRI) with multiple imputations, and the percentage of each missing covariables was below 10%.

Version 4.4.1 of R was employed to conduct all statistical analyses. This study defined statistical significance as ***P***-value < 0.05.

Results

Baseline characteristic

The basic characteristic of the studied populations were summed up in Table 1. The average age of 9725 persons in this study was 59.60 years, and 1065 of them had a chronic cough. In the comparison of people without chronic cough versus people with chronic cough, several variables exhibited statistically significant differences, such as race, age, education, marriage, smoking, hypertension, diabetes, CVD, asthma, emphysema, chronic bronchitis, cancer, SII, SIRI, and NHHR.

Association between NHHR and chronic cough

This research also employed three logistic regressions to quantify the association between NHHR with chronic cough (Table 2). Higher NHHR was associated with increased odds of chronic cough, as demonstrated by Models A, B, and C. And Model C showed the odds of chronic cough increased by 8% for each additional unit of NHHR, adjusting for all covariates. The results of the trend test (Table 2) indicated that the NHHR group with the highest tertile (T3) had an increased likelihood of chronic cough compared to the NHHR group with the lowest tertile (T1). The ***P*** for trend = 0.0216 indicated statistical significance in the trend test and suggested a linear association between NHHR and chronic cough. Subsequently, this study further confirmed the linear association between NHHR and chronic cough using RCS (***P***-non-linear = 0.160) (Fig. 2). Mediation analysis proved that SII (1.62%) and SIRI (2.97%) partially mediated the association between NHHR and the probability of chronic cough (Figure S1).

SHAP Model

Moreover, this study also used SHAP based on the XGBoost model to evaluate the contribution and importance of each variable (sex, age, race, education, marriage, BMI, smoking, alcohol, hypertension, diabetes, CVD, asthma, chronic bronchitis, emphysema, cancer, SII, SIRI, and NHHR) in predicting chronic cough. The SHAP model indicated that the top five variables that contributed the most to predicting chronic cough were SII, smoking, NHHR, BMI, and SIRI (Fig. 3A). Among them, NHHR was positively associated with chronic cough (Fig. 3B).

Subgroup and sensitivity analysis

Subgroup analyses were carried out to discuss the association between NHHR with chronic cough in various groups (Table S1). White women over 60 years old, without asthma, chronic bronchitis, or emphysema, exhibited the positive association between elevated NHHR with probability of chronic cough. This investigation also conducted several sensitivity analyses to prove the dependability and accuracy of previous outcomes. After the multiple imputation of all missing covariables, the primary results obtained from the imputed data were predominantly consistent with previous outcomes (Table S2 and Figure S2).

Discussion

Novel insights into the associations between NHHR and the probability of chronic cough were provided by our study. Multiple statistical models were employed in this study, revealing that the probability of chronic cough increased as NHHR levels rose. Mediation analysis proved that SII and SIRI partially mediated the association between NHHR and chronic cough. As evidently suggested by the SHAP model, SII, smoking, NHHR, BMI, and SIRI were identified as the top five key predictors for the probability of chronic cough.

The notion that NHHR is a superior indicator of lipid-relevant disease risk is strongly supported by mushrooming evidence. Although rare studies have directly dug into the possible link between a chronic cough and lipid metabolism for the time being, multitudinous studies have suggested that problems with regard to lipid metabolism can worsen respiratory diseases like COPD, asthma, and community-acquired pneumonia (CAP) [22]. In general, respiratory disorders are featured by airflow limitation and chronic airway inflammation. What's more, inflammation presents a profound association with disorders of lipid metabolism [23]. As apparently demonstrated by current theory, high levels of plasma free fatty acids (FFA) and LDL-C can transform into oxidized LDL, which damages lung tissues even more by causing oxidative stress and apoptosis for more damage [24]. And evidence suggests that oxidative stress may be a key factor in triggering the vicious cycle of chronic cough [25]. Airway wall thickening and airflow limitation can be precipitated by aberrant lipid accumulation within the airways, thereby exacerbating the risk of airway injury in parallel [26]. As displayed by a 5-year follow-up prospective cohort study, an augment of 100 mg in triglyceride levels revealed a certain link with a 42% elevation in mortality rates among COPD patients [27]. Another nationwide population study in Taiwan has demonstrated a 1.48-fold elevated risk of COPD in individuals suffering from hyperlipidaemia in comparison with those without hyperlipidaemia [12]. A potential association between asthma and dyslipidemia, especially with elevated triglyceride levels, is being pointed out by accumulating evidence. As clearly suggested by an exploratory study, dyslipidemia contributes to the pathogenesis

Table 1 Baseline characteristics of study populations

	Without chronic cough (*N* = 8660)	With chronic cough (*N* = 1065)	*P*-value
Sex (%)			0.1762
Female	52.67	49.24	
Male	47.33	50.76	
Age (years)	57.04 ± 0.2	58.75 ± 0.45	0.0005
Race (%)			< 0.0001
Other Race populations	16.18	11.00	
White populations	73.93	81.05	
Black populations	9.89	7.95	
Education (%)			< 0.0001
Less than high school	17.87	28.34	
High school	22.86	29.72	
More than high school	59.26	41.94	
Marriage (%)			0.0012
Married	64.66	56.42	
Single	31.17	37.86	
Living with a partner	4.17	5.72	
BMI (kg/m2)	29.07 ± 0.10	29.51 ± 0.28	0.1147
Alcohol intake (gm)	10.47 ± 0.55	11.90 ± 1.42	0.2948
Smoke (%)			< 0.0001
No	54.13	29.32	
Yes	45.87	70.68	
Hypertension (%)			< 0.0001
No	59.24	48.58	
Yes	40.76	51.42	
Diabetes (%)			0.0001
No	88.24	82.99	
Yes	11.76	17.01	
CVD (%)			< 0.0001
No	88.96	79.50	
Yes	11.04	20.50	
Asthma (%)			< 0.0001
No	89.09	72.13	
Yes	10.91	27.87	
Chronic bronchitis (%)			< 0.0001
No	95.03	79.76	
Yes	4.97	20.24	
Emphysema (%)			< 0.0001
No	98.32	87.30	
Yes	1.68	12.70	
Cancer (%)			0.0158
No	86.78	83.59	
Yes	13.22	16.41	
SII (1000 cells/uL)	479.17 (347.29,674.33)	544.00 (392.29,762.07)	< 0.0001
SIRI (1000 cells/uL)	1.03 (0.72,1.48)	1.21 (0.83,1.75)	0.0001
NHHR	2.81 (2.07,3.78)	3.00 (2.11,3.96)	0.0004

Note: Median and interquartile range (IQR) for continuous variables with non-normal distributions; mean ± standard error (SE) for continuous variables with normal distributions. Proportions were employed to describe categorical variables. SII: systemic immune inflammation index; SIRI: system inflammation response index; NHHR: non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio

of asthma. An independent association between elevated serum triglyceride levels and asthma in obese patients was reported accordingly [28]. It' s noteworthy that a link between composite biomarkers, such as the monocyte-to-HDL cholesterol ratio and the triglyceride-glucose index, has been shown by cross-sectional studies [29, 30]. The problem of lipid indices not fully describing fat utilization in organisms and the asthma patient

Table 2 Association between NHHR and chronic cough

	Model A	Model B	Model C
	OR (95% CI) *P*-value	**OR (95% CI) *P*-value**	**OR (95% CI) *P*-value**
NHHR	1.10 (1.05, 1.15) 0.0002	1.11 (1.06, 1.17) 0.0002	1.08 (1.02, 1.14) 0.0105
NHHR tertiles groups			
T1 (0.44–2.28)	Reference	Reference	Reference
T2 (2.29–3.41)	0.98 (0.80, 1.19) 0.8376	0.99 (0.80, 1.22) 0.9342	1.00 (0.78, 1.28) 0.9905
T3 (3.42–16.59)	1.34 (1.13, 1.60) 0.0019	1.40 (1.15, 1.70) 0.0016	1.27 (1.04, 1.56) 0.0274
***P*for trend**	0.0017	0.0015	0.0216

Note: Model A adjusted for none. Model B adjusted for sex, age, and race. Model C = Model B + adjusted for education, marriage, BMI, smoke, alcohol, hypertension, diabetes, CVD, asthma, chronic bronchitis, emphysema, cancer, SII, and SIRI

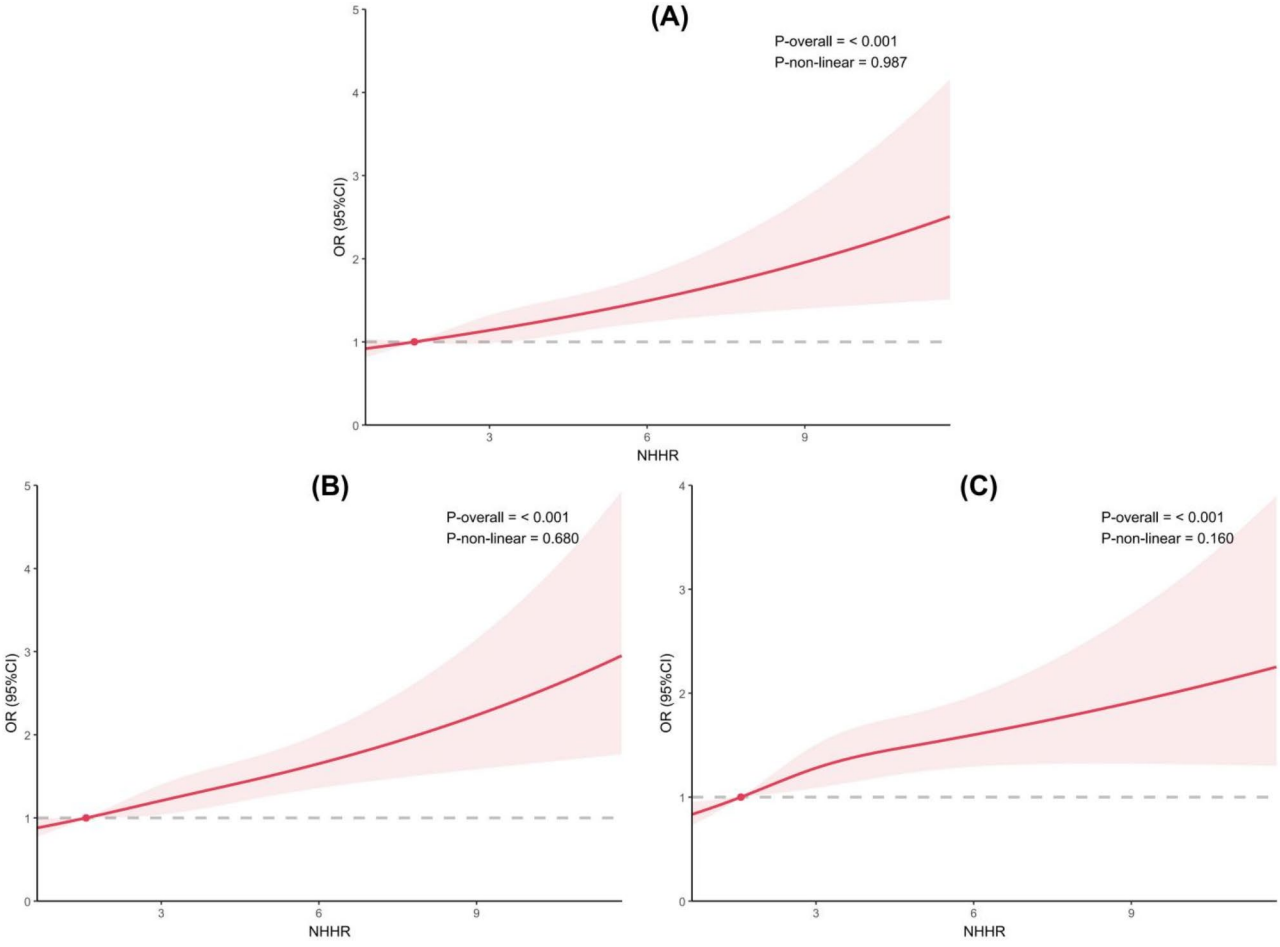

Fig. 2 Dose-response association of NHHR and chronic cough based on models A **(A)**, B **(B)**, and C **(C)**. Model A adjusted for none. Model B adjusted for sex, age, and race. Model C = Model Y + adjusted for education, marriage, BMI, smoking, alcohol, hypertension, diabetes, CVD, asthma, chronic bronchitis, emphysema, cancer, SII, and SIRI

population has been addressed by these studies. More recent retrospective analyses have unveiled a positive link between elevated levels of triglycerides, total cholesterol, and LDL-C being associated with the development of asthma [31]. As indicated by an all-round review of the literature on sepsis, plasma cholesterol is a paramount factor in severe bacterial infections [32]. On top of that, within the field of sepsis research, evidence in an increasing amount underscores the vital importance of plasma cholesterol in severe bacterial infections. A modest-scale investigation exhibits a major finding that hypocholesterolemia is linked with augmented mortality from severe CAP [33].

Respiratory conditions, such as chronic bronchitis (a type of COPD), asthma, and pathogenic infections, are widely recognized as common causes of chronic cough [34]. While numerous studies have suggested a potential link between dyslipidemia and respiratory conditions,

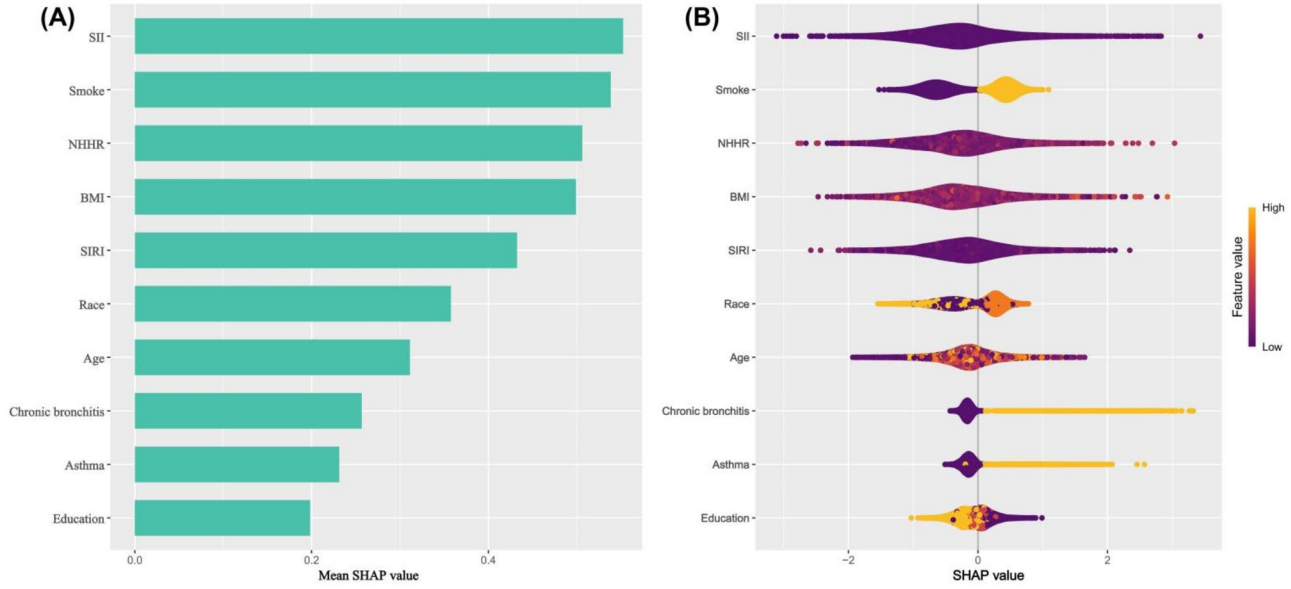

Fig. 3 The SHAP model based on XGBoost provided the relative importance of each variable on chronic cough

evidence remains limited. To date, only a small number of studies have directly explored the association between chronic cough and dyslipidemia. The study's findings, which delved into the lipid profiles of individuals with chronic cough, indicated that no statistically significant differences were found in cholesterol, triglyceride, VLDL, and HDL values when the patient group and the control group were compared systematically [35]. Nevertheless, our exploration suggested that NHHR displayed positive connection with an augmented prevalence of chronic cough.

NHHR stands for a new marker of blood lipid status. As evidently illustrated by a multiplying number of studies, NHHR can independently throw light upon the risk of lipid-relevant diseases in adults, including Non-alcoholic fatty liver disease, kidney stones, diabetes, and suicidal thoughts [36–39]. It has been proven true even when accounting for errors in LDL and HDL levels. A negative association between NHHR and asthma incidence was demonstrated among American people, with gender influences being noted [40]. We also observed that DII-mediated, higher NHHR levels can bring about an augment in COPD prevalence [41]. It's noteworthy that a linear positive association between NHHR and chronic cough was found in our investigation, which aligns with the conclusions drawn from their studies. As a result, NHHR serves as a valuable tool for predicting the likelihood of chronic cough. Altogether, excellent predictive efficacy has been demonstrated by the NHHR in a range of studies. Furthermore, distinguished by its non-invasive nature, ease of accessibility, and cost-effectiveness, the NHHR therefore has been extensively utilized, which adequately exhibits exceptional potential for clinical implementation.

Notwithstanding the fact that the link between NHHR and chronic cough through various statistical models, some limitations still exist in our survey. First and foremost, the diagnosis of chronic cough in NHANES is based on standard medical questionnaires rather than international diagnostic criteria, and some people lost questionnaire information, which may cause some bias. And due to database limitations, this survey did not include information on other potential chronic cough diseases, such as gastroesophageal reflux disease and interstitial lung disease. Secondly, we failed to prove causation as much attributable to the study's cross-sectional approach. It's exceedingly pivotal to carry out longitudinal studies, so as to confirm the causal link between NHHR and chronic cough. In addition, despite the adjustment for a wide range of covariables, the limitation inherent in NHANES data prevents the exclusion of potential confounders arising from unmeasured variables, such as dietary factors or occupational exposures. Last, certain drugs that affect chronic cough may have been excluded from the study population ascribed to the limitations of the NHANES database. Further studies incorporating clinical evaluations are needed to validate our results.

Conclusion

This study discovered that NHHR was positively associated with chronic cough. SII and SIRI partially mediated the association between NHHR and chronic cough. NHHR may be a valuable biomarker for predicting chronic cough. Regular NHHR monitoring may serve as

a potential tool for identifying individuals at higher risk of chronic cough.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02498-6.

Supplementary Material 1

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This investigation applied NHANES data and received approval from the NCHS Research Ethics Review Board (Protocol #2005-06, #2011-17).

Author contributions
Conceptualization: CFW, JW, XCL, YL; Data collection: CFW, XCL, JW; Statistical analysis: JW, CFW; Original draft: CFW, XCL, JLC, JW; Review & editing: JW, YL; Project administration: CFW, YL, JW.

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Data availability
The website (http://www.cdc.gov/nchs/nhanes/) contains all the data.

Declarations

Conflict of interest
All authors have reported that they have no conflicts of interest to disclose.

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