Lipids in Health and Disease

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Gender-specific association between a lipid composite index and asthma among US adults: insights from a population-based study

Bufan Ying[1†], Xiaoxin Liu[3†], Chengming Yang[1], Jinfang Xu[4*] and Ying Chen[2*]

Abstract

Background Abnormalities in lipid metabolism are common among adult asthmatics. However, the precise directionality linking asthma to blood lipid levels remains controversial. Our study aimed to evaluate the association between the Non-HDL to HDL Ratio (NHHR), a lipid composite index, and asthma prevalence among the adult population in the United States.

Methods Utilizing adult participants' data from the National Health and Nutrition Examination Survey (NHANES) spanning the years 2009 to 2018, the study employed a multivariable logistic regression model, adjusting for covariables, to establish the relationship between NHHR levels and the prevalence of asthma. Furthermore, smoothing curve fitting and subgroup analyses were conducted to investigate the robustness of this association.

Results This study included 26,023 adult individuals (mean age = 49.63 ± 17.66). In the fully adjusted model, a significant inverse association was observed between log-transformed NHHR values and asthma prevalence (OR = 0.85, 95% CI: 0.79–0.93). Subgroup analysis revealed that gender served as a modulator, altering the association between NHHR levels and asthma prevalence. A more pronounced negative association between lnNHHR and asthma prevalence was noted among male participants [(Male: OR = 0.78, 95% CI: 0.69–0.88) vs. (Female: OR = 0.92, 95% CI: 0.83–1.03), P for interaction = 0.0313].

Conclusions Our study revealed an inverse association between NHHR levels and the prevalence of asthma in the US adult population, which is influenced by gender. NHHR measurement may be a potential tool for early identification and prediction of adult asthmatics in specific populations.

Keywords NHANES, Asthma, Cross-sectional study, The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio

†Bufan Ying and Xiaoxin Liu contributed equally to this work.

*Correspondence:
Jinfang Xu
fangxjf@163.com
Ying Chen
ying.chen@tmu.edu.cn
[1]School of Basic Medical Sciences, Naval Medical University, No 800. Xiangyin Road, Yangpu, Shanghai 200433, China
[2]NHC Key Laboratory of Hormones and Development, Tianjin Key Laboratory of Metabolic Diseases, Chu Hsien-I Memorial Hospital & Tianjin Institute of Endocrinology, Tianjin Medical University, Tianjin 300134, China
[3]Department of Nephrology, Liyuan Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430077, Hubei, China
[4]Department of Health Statistics, Naval Medical University, No 800. Xiangyin Road, Yangpu, Shanghai 200433, China

Background

Asthma, a prevalent condition deeply rooted in chronic inflammation of the lower respiratory tract, stems from intricate and heterogeneous gene-environment interactions that are still not fully comprehended [1]. Marked by variable airway obstruction and bronchial hyperreactivity, it clinically presents with recurrent symptoms such as wheezing, coughing, chest tightness, and dyspnea [2]. Alarmingly, as of 2019, the global asthma population stood at approximately 262 million individuals [3], with a disproportionate burden observed in low- and middle-income countries. In these regions, the prevalence of asthma is particularly severe, exacerbated by the lack of accessible diagnostic tools and effective treatments [4]. This deficiency leads to a higher incidence of health complications and asthma-related fatalities, underscoring the urgent need for improved diagnosis and management strategies worldwide. Genome-wide studies have revealed that childhood-onset and adult-onset asthma share certain genetic loci. Still, the genetic influence of adult asthma is relatively small, suggesting that non-genetic factors may play a greater role in the development of adult asthma [5].

Abnormal alterations in high-density lipoprotein cholesterol (HDL-C) and total cholesterol (TC) levels, known as dyslipidemia, have been extensively established as a significant contributor to various chronic diseases [6, 7]. HDL-C serves a protective role in cardiovascular health [8], whereas elevated TC levels are indicative of increased risk for cardiovascular diseases [9]. In recent years, as the understanding of asthma pathogenesis deepens, a growing number of studies have begun to explore the potential associations between asthma and dyslipidemia.

Several investigations have revealed the presence of altered lipid profiles in asthma patients, with these changes potentially implicating inflammation, oxidative stress, and disruptions in lipid metabolism [10]. Nevertheless, the precise directionality and underlying mechanisms linking asthma to dyslipidemia remain controversial. Alexandra et al. identified a positive association linking elevated levels of triglycerides, TC, low-density lipoprotein cholesterol (LDL-C), and occurrence of asthma through a review of existing literature [11]. However, a study focusing on the US population yielded contrasting findings, demonstrating an inverse association between serum TC and non-HDL-C levels with asthma, while HDL-C levels did not differ significantly between groups, primarily reflecting the intricate interplay among metabolic abnormalities (MAs) [12]. Sole lipid indices may fall short of comprehensively elucidating lipid metabolism within an organism. Cross-sectional studies suggest an association between composite biomarkers, such as monocyte-to-high-density lipoprotein-cholesterol ratio [13] and Triglyceride-Glucose Index [14], and the prevalence of asthma.

Non-high-density Lipoprotein Cholesterol to High-density Lipoprotein Cholesterol Ratio (NHHR) is a novelly developed atherogenic lipid composite index, holistically encapsulating information on both atherogenic and anti-atherogenic lipid components [15]. Recent research has illuminated an association between NHHR and various health conditions, including kidney stone formation, mental well-being, and sleep quality [16–19]. Furthermore, Sheng et al. [20] have reported its predictive value in metabolic syndromes such as diabetes. Compared with conventional lipid parameters, NHHR has demonstrated potential utility in the recent investigation of chronic inflammatory diseases like periodontitis, underscoring its significance in a broader clinical context [21].

Despite the scarcity of large-scale population studies on the association between NHHR and asthma prevalence, we conducted a cross-sectional population-based survey utilizing NHANES data from 2009 to 2018 to investigate the link between NHHR and the prevalence of adult-onset asthma in the United States. Our ultimate goal is to develop a reliable blood lipid parameter as a predictive biomarker for asthma, which could significantly benefit asthma risk assessment and preventive strategies, catering to a wider asthmatic population.

Methods

Data source

This study analyzed the National Health and Nutrition Examination Survey (NHANES) data from 2009 to 2018, a nationally representative survey administered by the National Center for Health Statistics (NCHS) to assess health and nutrition in non-institutionalized US civilians. NHANES, embracing diverse ethnicities, explores health trends, nutrition, and sociological factors. The data acquisition process employed a rigorous multi-stage probability design, with ethical oversight by the Institutional Review Board (IRB) of NCHS, United States. Prior to participation, all individuals provided informed consent [22].

Adhering to STROBE guidelines, this study examined structured questionnaires, physical examinations, and laboratory tests supervised by NCHS, which are publicly available on the NHANES website. Detailed information regarding recruitment methodologies, procedural protocols, population demographics, and the overall study design of NHANES is comprehensively documented by the Centers for Disease Control and Prevention (CDC) [23].

Study population

Our investigation selected data from five NHANES survey cycles between 2009 and 2018. Initially, the cohort consisted of 49,693 individuals. We excluded 13,241 participants who lacked NHHR data, 32 participants with missing or unclear asthma history data, and 10,397 participants under the age of 20. For other missing covariables data, the multiple imputation method was employed. The detailed screening process of the study participants is visually depicted in Fig. 1. Ultimately, this study included 26,023 adult subjects (aged 20 years and above).

Definition of NHHR

Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) was designated as an exposure metric within our research framework, derived meticulously from the individual lipid profiles of participants. The computation adheres to the formula: NHHR = Non-HDL-C / HDL-C, where Non-HDL-C is derived by deducting high-density lipoprotein cholesterol

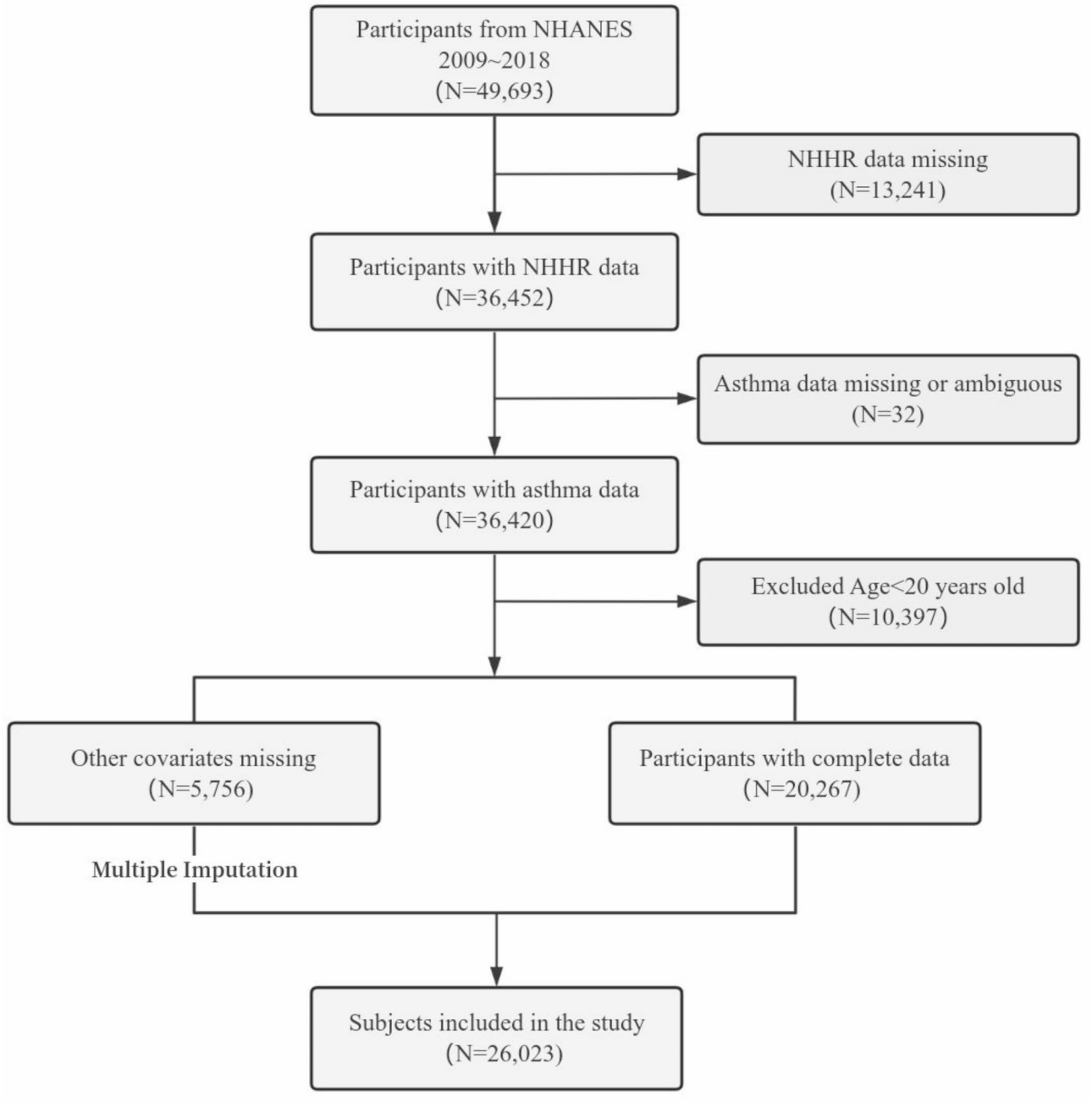

Fig. 1 Flow chart of sample screening

(HDL-C) from total cholesterol (TC) [24]. Blood samples were obtained in the morning session and participants were instructed to fast for 9 h. The enzymatic assay methodology, renowned for its precision, is employed in the laboratory to measure both total cholesterol and HDL-C accurately.

Assessment of asthma

The Global Initiative for Asthma (GINA) 2023 report has categorically defined asthma as variable airflow limitation, confirmed by ≥12% and ≥200 mL FEV1 improvement after bronchodilator use [25]. To evaluate the prevalence of asthma among participants, we utilized comprehensive data from the NHANES. These data included outcomes from health status questionnaires, specific indices from lung function tests, and medication history records. We based our identification of asthma patients on these existing data to conduct a secondary analysis.

The questionnaire was designed to elicit crucial information through the inquiry: "Has a medical practitioner or healthcare professional ever diagnosed you with asthma?" Utilizing this query as a cornerstone, along with the data from NHANES, we devised a classification system. Initially, individuals who affirmatively responded to this question or exhibited a positive outcome on a bronchodilator test conducted during spirometry, as reported in NHANES, were categorized as asthma patients. Additionally, individuals with no history of smoking, exclusion of COPD diagnosis, but who used anti-asthmatic medications, were also included within the asthma patient category.

Covariables

Drawing upon previous studies, potential confounding factors linked with NHHR and asthma were incorporated in the final analysis [26, 27]. Covariables included age, gender, race, educational level, marital status, Body Mass Index (BMI), Income to Poverty Ratio (PIR), physical exercise, family history of asthma, smoking and drinking status as well as medical history.

To facilitate data integration, the following variables were further categorized as:

1. Smoking status: Active Smokers (having smoked over one hundred cigarettes throughout their lives, or who are currently engaging in smoking on an occasional to daily basis); Passive Smokers (including former smokers [without a history of one hundred cigarettes throughout their lives] and individuals who do not smoke directly but are exposed to secondhand smoke due to living or working in environments where others smoke regularly); Non-Exposed Individuals (those with no history of smoking or secondhand smoke exposure).
2. Drinking status: Active Drinkers (having consumed over twelve alcoholic drinks in the past year or more frequently than once a month); Non-Active Drinkers (those who do not meet the criteria for active drinkers).
3. Physical exercise: Active Exercisers (Involving moderate-intensity activity in work that causes small increases in respiratory or cardiac rate for at least 10 min continuously or staying physically active at least 60 min weekly); Non-Active Exercisers (those who do not meet the criteria for active exercisers).
4. Diabetes mellitus: It was confirmed via a convergence of methods, including the diagnosis of a healthcare practitioner, measurement of fasting glucose levels (greater than or equal to 7.0 mmol/L), and the results of a two-hour oral glucose tolerance test (OGTT, ≥ 11.1 mmol/L) [28].
5. Hypertension: Its definition is based on participants' self-reported responses to the inquiry regarding whether they have ever been informed of having high blood pressure coupled with blood pressure measurements. Participants who exhibited an average systolic reading above 140 mmHg or an average diastolic reading higher than 90 mmHg across four separate examinations were classified as hypertensive patients.

Statistical analyses

The entire data processing and statistical analyses procedures were executed using R Studio (version 4.2.2) and EmpowerStats (version 2.0). NHHR values were categorized into quartiles, ranging from the lowest quartile (Q1) to the highest (Q4). To address the skewed distribution and relatively small values of NHHR, which may obscure effect sizes, we applied a natural logarithmic transformation (lnNHHR) to facilitate interpretation. Figure 2 illustrated the original distribution of NHHR alongside its logarithmic transformation. For missing data, the method of multiple imputation was employed to preserve the nature of the data. Continuous variables were presented as mean values plus or minus standard deviation (SD), while categorical variables were denoted as proportions. Statistical disparities between participants with or without asthma were assessed using either the Student's t-test (continuous variables) or the chi-square test (categorical variables).

The association between the NHHR levels and asthma prevalence was investigated using multivariable logistic regression models in which odds ratios (ORs) and their corresponding 95% confidence interval (95% CIs) were estimated. In model 1, an unadjusted analysis was

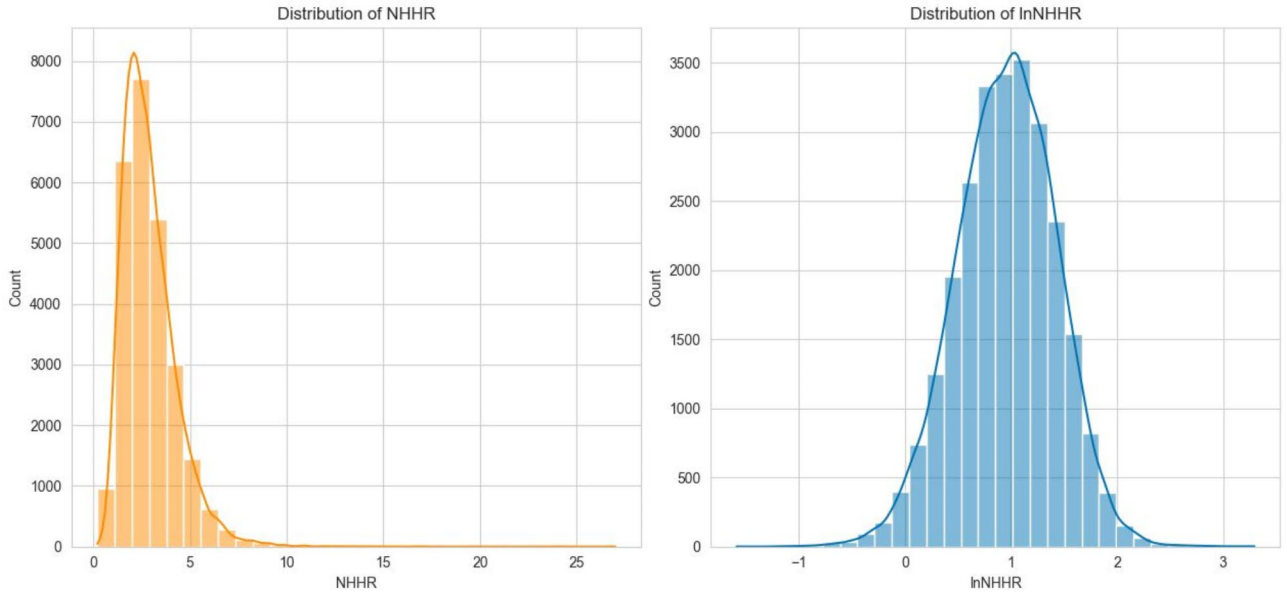

Fig. 2 Distribution of NHHR and log-transformed NHHR values

conducted, without incorporating any covariables. Subsequently, Model 2 was adjusted for basic demographic and physiological factors: age, gender, race, and Body Mass Index. Model 3 added more adjustments, including education level, marital status, income to poverty ratio, alcohol consumption status, smoking habit, and physical activity. Building upon Model 3, Model 4 incorporated further adjustments for covariables related to health status and disease history, such as hypertension, diabetes, and genetic predisposition to asthma. Four models were employed to construct multivariable tests, where variables were controlled, and a smooth curve was fitted.

Moreover, a profound subgroup analysis and interaction testing were performed, aiming to delve into potential disparities across diverse populations. To mitigate the notable fluctuations inherent in our dataset, we adopted a weighting methodology endorsed by the CDC [29].

Results

Baseline characteristics of participants

After data screening, 26,023 adult participants were enrolled to investigate the relationship between NHHR and asthma prevalence. Among these participants, 51.77% were female, and 65.86% were Non-Hispanic White. The average age of the adult participants was 49.63±17.66 years. The mean NHHR value among the adult participants was 2.90±1.44, with 3,824 individuals (14.69% of the total) reporting a history of asthma.

Table 1 presented the detailed characteristics of the participants, stratified by the presence of asthma. Statistically significant associations ($p<0.05$) were observed between the asthma status and multiple characteristics of adult participants, including but not limited to age, gender, race, marital status, smoking habits, body mass index (BMI), Income to poverty ratio (PIR), family history of asthma, diabetes status, hypertension status, total cholesterol levels, and NHHR values. Compared to the Non-Asthma group, the Asthma group was more likely to be female and younger. Additionally, asthmatics were more prone to having lower NHHR values and being obese (BMI≥30).

Association between NHHR and asthma

Given the skewed distribution of NHHR values and the inconspicuous effect value, a logarithmic transformation was considered, employing lnNHHR for analysis. This approach rectified the skewed data, bringing it closer to a normal distribution. Multivariable regression analysis was subsequently conducted to explore the association between NHHR variations and asthma prevalence, with the results presented in Table 2. In Model 1, a significant inverse relationship was observed between lnNHHR and asthma prevalence, with an OR of 0.90 (95% CI: 0.84–0.97). After incorporating basic demographic and physiological characteristic covariables, the value of OR was found to be 0.88 (95% CI: 0.81–0.96), indicating a statistically significant effect. In the fully adjusted model, accounting for all 13 covariables, a distinct negative association persisted between lnNHHR and asthma prevalence (OR=0.85, 95% CI: 0.79–0.93). These results demonstrated that as we progressively incorporated additional covariables, the OR values exhibited a downward trend. Consistency was observed across the four models in terms of their outcomes.

Furthermore, a sensitivity analysis was performed using quartiles of lnNHHR as a stratified variable. This analysis

Table 1 Weighted characteristics of the study population based on asthma

Characteristics	Total *N* = 26,023	Non-Asthma *N* = 22,199	Asthma *N* = 3,824	*P*-value
Age (years)	49.63 ± 17.66	49.95 ± 17.62	47.76 ± 17.77	< 0.001
Gender, n(%)				< 0.001
Male	12,585 (48.23)	10,998 (49.57)	1587 (40.60)	
Female	13,438 (51.77)	11,201 (50.43)	2237 (59.40)	
Race, n(%)				< 0.001
Mexican American	3856 (8.73)	3497 (9.26)	359 (5.72)	
Other Hispanic	2714 (6.10)	2304 (6.09)	410 (6.18)	
Non-Hispanic White	10,380 (65.86)	8711 (65.59)	1669 (67.42)	
Non-Hispanic Black	5438 (10.82)	4499 (10.47)	939 (12.79)	
Other Race	3635 (8.49)	3188 (8.59)	447 (7.89)	
Education status, n(%)				0.108
< High school	6103 (15.15)	5307 (15.36)	796 (13.95)	
High school graduate	5832 (22.58)	4980 (22.73)	852 (21.69)	
≥College	14,088 (62.27)	11,912 (61.91)	2176 (64.36)	
Marital status, n(%)				< 0.001
Married/Living with partners	15,429 (63.23)	13,412 (64.31)	2017 (57.08)	
Separated/Divorced/Widowed	5763 (18.43)	4818 (18.05)	945 (20.61)	
Never married	4831 (18.34)	3969 (17.64)	862 (22.31)	
Alcohol consumption status, n(%)				0.689
Active Drinkers	17,421 (73.06)	14,794 (73.00)	2627 (73.42)	
Non-Active Drinkers	8602 (26.94)	7405 (27.00)	1197 (26.58)	
Smoking status, n(%)				< 0.001
Non-Exposed Individuals	12,231 (47.37)	10,698 (48.31)	1533 (42.07)	
Active Smokers	11,321 (43.72)	9422 (42.83)	1899 (48.80)	
Passive Smokers	2471 (8.90)	2079 (8.86)	392 (9.13)	
Diabetes mellitus (DM), n(%)				0.017
No	19,181 (77.90)	16,455 (78.16)	2726 (76.42)	
Pre-DM (IFG/IGT)	2464 (9.34)	2112 (9.40)	352 (8.97)	
DM	4378 (12.76)	3632 (12.43)	746 (14.61)	
Hypertension, n(%)				< 0.001
Yes	11,054 (37.67)	9264 (36.95)	1790 (41.78)	
No	14,969 (62.33)	12,935 (63.05)	2034 (58.22)	
Physical exercise, n(%)				0.380
Active Exercisers	13,232 (56.53)	11,221 (56.37)	2011 (57.47)	
Non-Active Exercisers	12,791 (43.47)	10,978 (43.63)	1813 (42.53)	
Close relatives with asthma, n(%)				< 0.001
Yes	5243 (20.68)	3659 (17.10)	1584 (41.10)	
No	20,780 (79.32)	18,540 (82.90)	2240 (58.90)	
Income to poverty ratio, n(%)				< 0.001
< 1.3	8015 (21.10)	6618 (20.19)	1397 (26.27)	
≥ 1.3, < 3.5	10,660 (37.79)	9192 (37.89)	1468 (37.24)	
≥ 3.5	7348 (41.11)	6389 (41.92)	959 (36.49)	
BMI (kg/m^2), n(%)				< 0.001
< 18.5	404 (1.53)	347 (1.53)	57 (1.57)	
≥ 18.5, < 25	6926 (27.08)	6047 (27.43)	879 (25.08)	
≥ 25, < 30	8551 (32.94)	7479 (33.71)	1072 (28.56)	
≥ 30	10,142 (38.45)	8326 (37.34)	1816 (44.80)	
HDL-C (mg/dL)	53.07 ± 16.20	53.05 ± 16.11	53.20 ± 16.73	0.972
Total cholesterol (TC) (mg/dL)	191.35 ± 41.71	191.74 ± 41.51	188.32 ± 42.79	< 0.001
NHHR	2.90 ± 1.44	2.91 ± 1.43	2.85 ± 1.49	0.005
lnNHHR	0.95 ± 0.47	0.96 ± 0.47	0.93 ± 0.48	0.005

Mean ± SD for continuous variables: P value was derived from a weighted linear regression analysis

% for categorical variables: P value was computed using a weighted chi-square test

Table 2 The association between lnNHHR and asthma

Exposure	Crude Model	Partially Adjusted Model	Partially Adjusted Model	Fully Adjusted Model
	(Model 1)	(Model 2)	(Model 3)	(Model 4)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
lnNHHR	0.90 (0.84, 0.97)**	0.88 (0.81, 0.96)**	0.87 (0.80, 0.94)***	0.85 (0.79, 0.93)***
lnNHHR quartiles				
Q1	Reference	Reference	Reference	Reference
Q2	0.94 (0.86, 1.04)	0.91 (0.83, 1.01)	0.92 (0.83, 1.01)	0.92 (0.83, 1.02)
Q3	0.86 (0.78, 0.95)**	0.84 (0.76, 0.93)***	0.84 (0.76, 0.93)***	0.83 (0.75, 0.93)***
Q4	0.89 (0.81, 0.98)*	0.87 (0.78, 0.97)**	0.85 (0.76, 0.94)**	0.84 (0.75, 0.94)**

* $p<0.05$, ** $p<0.01$, *** $p<0.001$; a p-value less than 0.05 is considered statistically significant

Model 1: No covariables were adjusted

Model 2: Age, gender, race, and Body Mass Index (BMI) were adjusted

Model 3: Building upon Model 2, further adjustments were included for education status, marital status, Income to Poverty Ratio (PIR), smoking and drinking status, and physical exercise

Model 4: Building upon Model 3, further adjustments were included for hypertension, diabetes, and family history of asthma

NHHR, Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OR, odds ratio; 95% CI, 95% confidence interval

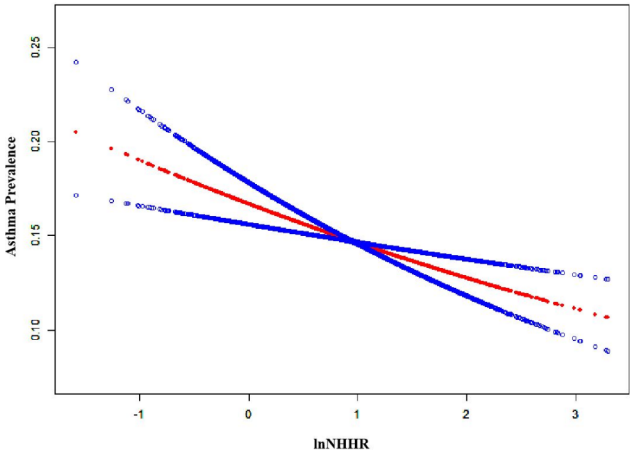

Fig. 3 The association between lnNHHR and asthma. All the covariables were adjusted. The solid red line depicts a smooth curve fitting the relationship between variables, while the blue bands encapsulate the 95% confidence interval associated with this fit

revealed that individuals within the highest quartile (Q4) portrayed a 16% reduced association with asthma prevalence compared to those in the lowest quartile (Q1), with an OR of 0.84 (95% CI: 0.75–0.94).

The curve-fitting analysis further portrayed a negative association between log-transformed NHHR values and asthma prevalence in adults, indicating that a decline in NHHR level corresponded to an elevated possibility of asthma (Fig. 3).

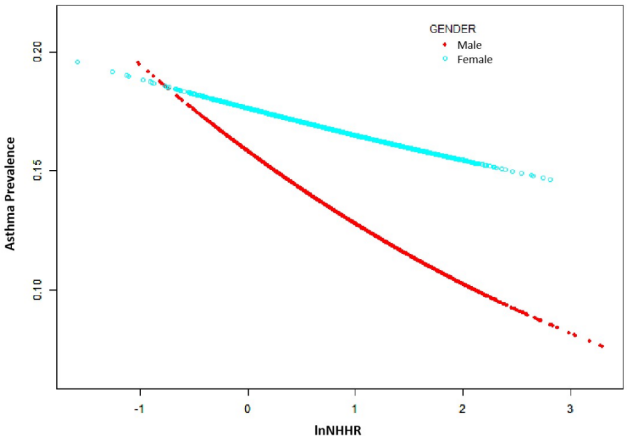

Fig. 4 The association between lnNHHR and asthma stratified by sex. All the covariables were adjusted. The red line demonstrates the association between NHHR and asthma among male individuals. The blue-green line depicts the association between NHHR and asthma among females

Subgroup analysis

The findings of this study revealed an inconsistent association between NHHR and asthma. Upon subgroup analysis, a significant interaction effect of NHHR values on asthma was observed within gender subgroups, with a more pronounced negative association between lnNHHR and asthma prevalence among male participants [(Male: OR=0.78, 95% CI: 0.69–0.88) vs. (Female: OR=0.92, 95% CI: 0.83–1.03), $P_{inter}<0.05$]. The association between lnNHHR levels and the prevalence of asthma among different genders was presented in Fig. 4. Notably, a significant relationship between NHHR and asthma prevalence was observed specifically among male subjects, different age groups (within the ranges of 20–40 years old and ≥60 years old) as well as BMI (between 18.5 and 30), as shown in Fig. 5.

Discussion

This study analyzed adult population data from the NHANES database for five cycles between 2009 and 2018 in order to explore the association between non-HDL cholesterol to HDL cholesterol ratio (NHHR) levels and asthma in adults. The findings of this research indicated that NHHR was negatively associated with the prevalence of asthma in adults. Additionally, the asthmatic group exhibited significantly lower total cholesterol (TC) levels compared to the non-asthma control group ($p<0.001$). In contrast, no significant difference was discerned in the concentrations of high-density lipoprotein cholesterol (HDL-C) between the two groups ($p=0.972$). This suggested that traditional lipid markers may not adequately capture the intricate nature of lipid metabolism in asthma. Consequently, we focused on the NHHR value as a more specific and comprehensive indicator of lipid abnormalities associated with asthma. This ratio takes

Characteristics	OR(95% CI)	P for interaction
Sex		0.0313
Male	0.78 (0.69, 0.88)	
Female	0.92 (0.83, 1.03)	
Age (years)		0.4998
⩾20, <40	0.86 (0.76, 0.98)	
⩾40, <60	0.92 (0.80, 1.06)	
⩾60	0.82 (0.71, 0.95)	
BMI		0.1195
<18.5	0.77 (0.37, 1.61)	
⩾18.5, <25	0.80 (0.68, 0.94)	
⩾25, <30	0.77 (0.67, 0.89)	
⩾30	0.95 (0.84, 1.08)	
PIR		0.4117
<1.3	0.82 (0.72, 0.94)	
⩾1.3, <3.5	0.91 (0.80, 1.03)	
⩾3.5	0.82 (0.70, 0.96)	
Smoking status		0.7143
Non-Exposed Individuals	0.83 (0.73, 0.94)	
Active Smokers	0.86 (0.77, 0.96)	
Passive Smokers	0.92 (0.73, 1.17)	
Hypertension		0.5085
Yes	0.83 (0.74, 0.93)	
No	0.88 (0.78, 0.98)	

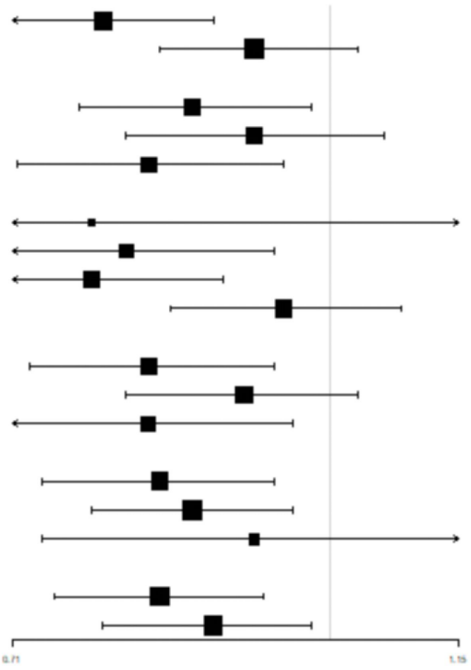

Fig. 5 Subgroup analysis for the association between lnNHHR and asthma, population-weighted. OR, odds ratio; 95% CI, 95% confidence interval

into account the relative relationship between all lipoprotein cholesterol fractions other than HDL-C (including low-density lipoprotein cholesterol and very low-density lipoprotein cholesterol) and HDL-C, thus providing a more holistic assessment of lipid status than individual lipoprotein levels. Despite the lack of significant difference in HDL-C levels between the groups, variations in non-HDL-C levels are amplified through the NHHR, revealing potential abnormalities in lipid metabolism or chronic inflammatory responses [20, 21].

In contrast to most previous studies that have mainly focused on the association between a single lipid component and asthma, the present study is the first to correlate the NHHR, a composite lipid marker, with the prevalence of asthma. The results of this investigation are consistent with some of the findings in previous literature. Michael et al. analyzed serum cholesterol measurements from 7,005 participants in the 2005–2006 National Health and Nutrition Examination Survey. They found that serum TC and non-HDL-C levels were negatively correlated with the prevalence of asthma, whereas HDL-C levels were not significantly correlated with asthma [12].

Abnormalities in lipid metabolism are common among asthmatics and are associated with the onset and progression of asthma [30, 31]. Wang et al. analyzed plasma samples from 20 healthy controls and 24 asthma patients. Differences in glycerophosphatidylcholine (gp) metabolites were found between asthmatics and healthy individuals [32]. There is a close relationship between the glycerophosphate metabolic pathway and the transport and metabolism of HDL-C. The phospholipids in HDL particles are mainly derived from the metabolic process of glycerophospholipids. Abnormal glycerophospholipid metabolism may affect the stability and function of HDL [33], which in turn affects asthma. Despite some studies speculating that there is a potential negative effect of HDL on ILC2-mediated inflammatory responses [34], Yao et al. employed the enzyme-linked immunosorbent assay (ELISA) technique to quantify the levels of serum amyloid A (SAA) in both asthmatic patients and non-asthmatic subjects. Their findings revealed that when HDL-C binds to SAA, it transforms into dysfunctional granules that exhibit proinflammatory properties. Cytokines such as IL-6, TNF-α, and IL-1b secreted by monocytes were stimulated by FPR2/ATP/P2×7R axis [35].

Besides HDL-C, NHDL (non-HDL cholesterol) is also a crucial factor influencing NHHR values, as it provides a comprehensive reflection of various lipid parameters including low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and apolipoprotein A (ApoA). Cellular and animal model evidence suggests that LDL, the predominant lipoprotein component of NHDL, may contribute to reduced asthma risk. LDL is efficiently absorbed in the lungs and subsequently induces a series of functional responses in lung-resident cells [36]. In this process, LDL exhibits an

inhibitory effect on TGF-β [37], a central mediator in asthma pathology, thereby indirectly modulating asthma-related reactions. Furthermore, a study conducted by Schulman et al. has shown that LDL can suppress human lung mast cells' ability to release histamine and diminish its biological effects [38]. Moreover, several studies have illuminated the defensive functions of apoA-I and apoE in asthma. To harness their therapeutic benefits, an array of apoA-I mimetic peptides have been devised and scrutinized for their ability to mitigate respiratory ailments, demonstrating anti-inflammatory and antioxidant effects [39].

However, some results of previous studies on blood lipid levels are inconsistent with our results. Liu et al. conducted a bidirectional two-sample Mendelian randomization study based on data from 24,853 Asian individuals, with an average age of 48.8 years. A causal relationship was found between elevated LDL and TC levels, decreased HDL levels and increased risk of asthma [40]. One of the primary reasons for such differences could be the distinct characteristics of the study populations. Stanesby et al. [41] quantified the tracking of blood lipid levels from childhood, adolescence to adulthood, revealing that the tracking coefficients for LDL-C, TC, HDL-C, and triglycerides (TG) varied across different age groups. By analyzing the plasma lipid metabolic profiles of asthmatic children and adults, it was shown that adult asthmatics exhibited a greater diversity of differentially expressed lipid molecules, suggesting that adult-onset asthma may be more reliant on alterations in lipid metabolism [31].

Meanwhile, a prospective cohort study involving 477 consecutive asthmatics, highlighted that the existence of various asthma phenotypes could be another contributing factor to the disparities in the results observed. The results showed that non-allergic phenotypes were associated with elevated TC levels, the obesity-related asthmatic type was associated with high TG, and the severe asthmatic type was associated with high LDL-C [42].

Subgroup analysis and interaction tests revealed that gender modified the relationship between NHHR levels and asthma prevalence. Specifically, the inverse association between NHHR levels and asthma prevalence was more pronounced among men. Clinical observations have shown that the incidence of asthma among males after puberty is notably lower than that in females, coinciding with the rise in male testosterone levels [43]. Radzikowska et al. found that serum testosterone levels exhibit a negative associstion with the incidence of asthma in both females and males [44], indicating that a lower level of testosterone is associated with a higher prevalence of asthma. Testosterone has been demonstrated to possess immunoregulatory functions, modulating calcium and potassium channel activity which would reduce excessive smooth muscle contraction [45], and inhibiting Th1 cell activation [46]. Studies have also found that variations in estrogen levels are associated with exacerbations of asthma symptoms during menstruation, pregnancy, and menopause [44]. Cholesterol levels influence airway smooth muscle contractility through estrogen [47]. Progesterone, estrogen, and their metabolites, after binding to human tissue protein, may act as antigens and promote Type 2 helper cell development, which in turn regulates antibody synthesis and allergies [48]. These phenomena suggest that changes in sex hormone levels may impact lipid metabolism and immune responses, ultimately leading to distinct biological effects and asthma prevalence associated with NHHR values between males and females. Concurrently, epigenetic studies have revealed that the level of DNA methylation at the 17q12-q21 locus is higher in females than in males [49], suggesting that gender-related epigenetic variations may influence susceptibility to asthma.

Strength

This study has demonstrated several strengths, the first being the large sample size, which is nationally representative. At the data processing level, we implemented a correction measure to ensure the rationality of data distribution, aiming at the skewed distribution characteristics of NHHR values. Facing the problem of missing covariable data, we applied the multiple imputation method. This strategy enhances the precision and validity of the estimation and enables the statistical inference to capture the real variability and uncertainty in the data more accurately. In addition, by employing a weighted model that focused on the oversampling of minorities, we further enhanced the reliability of our findings.

Limitations

Despite the positive developments of the study on several fronts, we are also aware of its limitations. The data related to asthma in the NHANES database were mainly obtained through questionnaires. Although we considered medication histories and pulmonary function test results, there were still subjective factors interfering, which might have led to the strength of the associations between the two being underestimated. Of particular significance, this study was based on a cross-sectional design, which only suggested that NHHR values are associated with asthma prevalence and did not allow for causal inferences.

Conclusion

Our study suggests a negative association between NHHR levels and the prevalence of asthma, which is modulated by gender. These findings underscored the potential clinical utility of NHHR, a lipid biomarker, in

identifying and predicting adult asthmatics in specific populations, thereby providing evidence for the exploration of the association between blood lipid levels and asthma. However, it is important to note that the results are derived from a cross-sectional study, which inherently limits our ability to establish causality. To address this limitation and advance our understanding, extensive prospective studies are warranted.

Abbreviations

NHANES	National Health and Nutrition Examination Survey
NHHR	Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio
BMI	Body mass index
PIR	Income to poverty ratio
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol

Acknowledgements
With profound gratitude, we acknowledge the invaluable support of Naval Medical University, whose dedication to medical excellence has been instrumental in the success of this study. Additionally, we extend our heartfelt thanks to the participants of the National Health and Nutrition Examination Survey, whose selfless contributions have enriched our understanding and illuminated the path forward.

Author contributions
Y.B.F. and L.X.X. designed the study, and were the major contributors in writing the manuscript. Y.C.M. analyzed and interpreted the participants' baseline characteristics. X.J.F. and C.Y. contributed to the revision of the manuscript.

Funding
This study was supported by the National Key R&D Program of China (2018YFC200194-02) and the Scientific Research Funding of Tianjin Medical University Chu Hsien-I Memorial Hospital (ZXY-YJJ2023-2).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The human-centric components of this research, encompassing participant involvement, utilization of human-derived materials, and analysis of human data, adhered strictly to the ethical principles outlined in the Declaration of Helsinki. Moreover, these aspects were granted approval by the Ethics Review Board of the NCHS, ensuring their compliance with ethical standards. Notably, all patients and participants voluntarily provided their written informed consent, signifying their agreement to take part in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 17 August 2024 / Accepted: 22 October 2024
Published online: 30 October 2024

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