

# Association between Non-High-Density Lipoprotein Cholesterol to High-Density Lipoprotein Cholesterol Ratio (NHHR) and Obstructive Sleep Apnea (OSA): A Cross-Sectional Study of the U.S. Population from 2015-2018

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## Abstract

**Objective:** The relationship between non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and the prevalence of obstructive sleep apnea (OSA) remains unclear. This investigation examines the potential relationship between NHHR and the prevalence of OSA in the broader, non-pregnant United States population. **Methods:** This investigation utilized data from the NHANES 2015-2018 dataset, employing a suite of statistical techniques, including univariate and multivariate logistic regression models, curve fitting, threshold effect analysis, subgroup analysis, and interaction tests, to examine the association between NHHR and the prevalence of OSA. **Results:** The research encompassed 5113 subjects, finding that nearly half (49.27%) were affected by Obstructive Sleep Apnea (OSA). The analysis used multivariate logistic regression to reveal a statistically significant positive association between NHHR and OSA. This was observed when NHHR was considered a continuous variable (OR = 1.07, 95% CI: 1.01 - 1.13,  $p = 0.0188$ ) across all models, including the crude model, model 1, and model 2. Furthermore, when NHHR was categorized into thirds, the highest tertile demonstrated a notably stronger correlation with OSA compared to the lowest tertile in the fully adjusted model 2 (OR = 1.45, 95% CI: 1.20 - 1.76,  $p = 0.0001$ ). Subgroup analysis highlighted that NHHR had a more pronounced ability to pre-

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dict the risk of OSA in females ( $p < 0.05$ ). Additionally, a nonlinear relationship between NHHR and OSA prevalence was identified through curve fitting and threshold effect analysis, pinpointing an inflection point at 3.65. **Conclusion:** Our understanding of the prevention and treatment of OSA may be improved by more research on NHHR, as our cross-sectional study suggested a potential nonlinear relationship between NHHR and OSA prevalence. To validate these results, more study is necessary.

### Keywords

Non-High-Density Lipoprotein Cholesterol to High-Density Lipoprotein Cholesterol Ratio, OSA, NHANES, Cross-Sectional Study

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## 1. Introduction

Obstructive sleep apnea (OSA) is a recurrent chronic illness marked by partial or total blockage of the upper respiratory tract while you sleep [1] [2]. It usually presents with nonspecific symptoms such as snoring, excessive daytime sleepiness or fatigue, and apnea [3]. These respiratory disturbances lead to periodic decreases or cessation of ventilation, which results in intermittent hypoxemia, hypercapnia, sleep fragmentation, recurrent nocturnal sleep awakenings, and activation of the sympathetic nervous system [4]. There is a close interplay between OSA and the oral cavity. As an important part of the upper respiratory tract, structural and functional abnormalities in the oral cavity may increase the risk of OSA, including anatomical abnormalities [5], mouth breathing habits [6], sleep grinding [7], and genetic factors [8]. In turn, OSA may adversely affect oral health, such as symptoms of congestion, masticatory muscle hypertrophy, and dry mouth [9], and long-term OSA may also aggravate diseases such as periodontitis [10].

An epidemiological investigation and a seminal article on the natural history of sleep cardiorespiratory disorders were published in 1993 by the researcher. This study revealed the high prevalence of untreated obstructive sleep apnea (OSA), which is important in the field of public health [11]. Since 2000, the number of people treated for OSA has continued to increase globally; In 2015, the United States, grappling with a widespread incidence of OSA, incurred an estimated \$12.4 billion in expenses related to the diagnosis and management of the condition, with half of the cost spent on therapeutic oral appliances and positive airway pressure (PAP) therapy, and the other half spent on surgical aspects of treatment [12]. Recent findings reveal that OSA has a widespread impact, afflicting close to one billion individuals worldwide, with an estimated 936 million adults grappling with varying degrees of this condition, from mild to severe [13], which poses a serious threat to public health worldwide. In addition, if left untreated, OSA may eventually lead to serious complications such as hypertension, cardiovascular disease, metabolic syndrome, and diabetes [14]-[18]. Currently, in clinical practice we widely consider polysomnography (PSG) as the gold standard for diagnosing

OSAHS [19], however obtaining PSG results can be challenging in some settings. For example, PSG monitoring equipment and sleep monitoring rooms may not be available in primary health care settings, and results may not be returned promptly when the subjects are children, as PSG examinations require them to sleep through the night. Therefore, finding a simple, easily accessible biomarker that is consistent with PSG results is critical for the early diagnosis of OSA, which can help clinicians make an initial assessment of the condition and plan subsequent treatment.

High-density lipoprotein cholesterol (HDL-C) is believed to have anti-inflammatory and anti-oxidative stress properties, which can help remove oxidative stress products and inflammatory mediators from the body [20]-[23]. In addition, HDL-C plays a crucial role throughout the cardiovascular system with anti-atherosclerotic, antiplatelet, and antithrombotic effects, protecting our cardiovascular system through a series of complex mechanisms [24]-[28]. A significant correlation exists between the severity of obstructive sleep apnea (OSA) and levels of HDL-C [29] [30]. The calculation of non-high-density lipoprotein (NHDL) cholesterol involves subtracting HDL-C from the total cholesterol (TC), providing a measure of the cholesterol content not carried by HDL particles and includes all cholesterol present in lipoprotein particles thought to cause atherosclerosis: triglyceride-rich (TG) lipoproteins, low-density lipoproteins, very low-density lipoproteins (VLDL), chyme residue, and intermediate-density lipoprotein (IDL) [31]. The non-high-density lipoprotein (NHDL) cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio (NHHR) has been identified as a novel atherosclerosis risk assessment index [32] [33]. In addition, a multitude of research has demonstrated that NHHR outperforms traditional lipid metrics in forecasting the likelihood of various diseases, showcasing its superior diagnostic precision, including atherosclerosis, abdominal aortic aneurysm, periodontitis, depression, non-alcoholic-fatty-liver-disease, diabetes, and metabolic syndrome [32] [34]-[39]. With these findings, we postulated whether NHHR could be utilized for early OSA diagnosis in high-risk individuals, allowing for the early implementation of interventions aimed at slowing the disease's advancement.

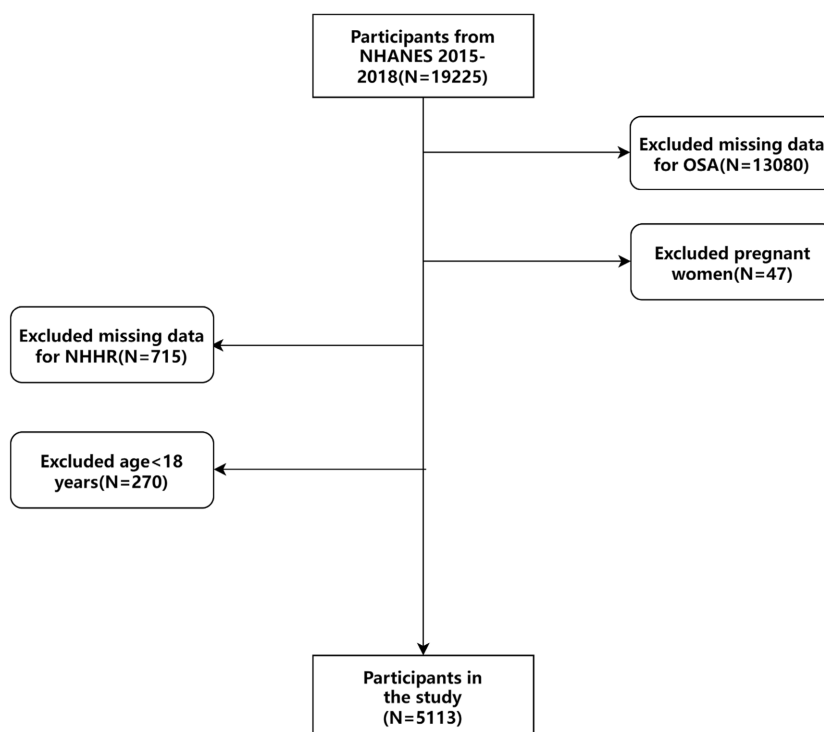
To the best of our knowledge, the potential connection between the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and obstructive sleep apnea (OSA) remains uncharted territory. We hypothesized that NHHR might be linked to OSA and that its regulation could play a role in the prevention and management of the condition. To explore this intriguing hypothesis, we initiated a cross-sectional investigation, utilizing data from the NHANES 2015-2018. We aimed to delve into the association between NHHR and the prevalence of obstructive sleep apnea within the non-pregnant United States population.

## 2. Materials and Methods

### 2.1. Research Participants and Data Collection

The data used in this cross-sectional survey come from NHANES 2015-2018,

which is strategically crafted to evaluate the health and nutritional status of the adult and pediatric populations across the United States. The survey includes data related to demographics, diet, screening, laboratory and questionnaires, and restricted access. For more information about the NHANES database, visit <https://www.cdc.gov/nchs/nhanes/index.htm>. There were 19,225 participants in the NHANES between 2015 and 2018. The study's sample size was then whittled down to 5113 participants by the application of exclusion criteria. Exclusion criteria included participants with missing OSA data (13,080), participants with missing NHHR levels ( $n = 715$ ), participants younger than 18 years of age ( $n = 270$ ), and pregnant women ( $n = 47$ ), and a flowchart of the population screening process is shown in **Figure 1**. The NHANES investigation secured the green light from the Ethics Review Board at the National Center for Health Statistics, affirming its strict adherence to ethical principles and protocols. Moreover, every participant willingly signed a written informed consent, highlighting the study's dedication to upholding ethical research standards, safeguarding participant rights, and maintaining confidentiality.



NHANES, National Health and Nutrition Examination Survey; OSA, obstructive sleep apnea syndrome; NHHR, non-high-density lipoprotein (NHDL) cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio.

**Figure 1.** Flow chart of the study design and participants excluded from the study.

## 2.2. Evaluation of Obstructive Sleep Apnea Syndrome (OSA)

A prior study said that an individual was diagnosed with OSA if they responded “yes” to any one of the following three NHANES questions [40]: 1) Experiencing

excessive daytime sleepiness between 16 to 30 instances in the past month, despite obtaining a minimum of seven hours of sleep nightly on weekdays or work nights; 2) Undergoing episodes of wheezing or respiratory cessation on three or more nights each week; and 3) Engaging in frequent snoring, occurring on three or more nights per week.

### 2.3. Calculation of NHHR

In this cross-sectional study, NHHR was specifically constructed as an exposure variable. The data sources for NHHR calculations are laboratory data called “HDL” and “TCHOL” in NHANES. “HDL-doc” provides high cholesterol lipoprotein density (HDL-C) data, while “TCHOL.doc” provides total cholesterol (TC) data. To compute the NHHR data, one begins by deducting the HDL-C levels from the total cholesterol (TC), yielding the non-high-density lipoprotein (NHDL) cholesterol figure. This result is then divided by the HDL-C levels, completing the calculation process [41].

### 2.4. Assessment of Covariates

In conjunction with previous research investigations and clinical analyses [42] [43], the following covariates were selected for adjustment in this cross-sectional study to explore the relationship between NHHR and OSA; The demographic variables assessed included age (years), race/ethnicity, gender (male/female), marital status, education level, and the household poverty-to-income ratio (PIR). The study delineated racial and ethnic groups into five distinct categories: Mexican American, non-Hispanic black, non-Hispanic white, Other Hispanic, and Other Race. Education levels were stratified into three classifications: below high school, high school, and college or above. Furthermore, marital status was segmented into three groups: never married, married/living with a partner, and widowed/separated/divorced. Family income poverty ratios (PIR) were categorized as low (less than \$14,500), medium (\$14,600 to \$32,300), and high (\$32,500 to \$50,000). body mass index (BMI) and WAIST are among the items examined in the NHANES database. BMI was determined by dividing an individual’s weight in kilograms by their height in meters squared. This metric is then segmented into four categories: <25.0, [25.0, 30.0), [30.0, 40.0), and  $\geq 40.0$ , with some studies suggesting that a BMI  $\geq 40$  kg/m<sup>2</sup> is morbidly obese [44] [45]. The questionnaires included drinking status, smoking status, sleep duration, monthly frequency of sleepiness, diabetes, and hypertension. Drinking status was determined by the question “How often have you had a drink in the last twelve months?” and the determination of smoking status was based on the question, “Have you smoked at least 100 cigarettes in your lifetime?” This criterion serves as a benchmark to identify individuals with a history of smoking [46]. Sleep duration was categorized as insufficient sleep (<7 h/d), recommended sleep (7 - 9 h/d), and excessive sleep (>9 h/d) [47]. Hypertension (HBP) and diabetes mellitus could be identified by subject self-report diagnosed by healthcare professionals.

## 2.5. Statistical Analysis

Data from NHANES were extracted, merged, cleaned, and statistically analyzed using R software (versions 3.4.3 and 4.2.0) and EmpowerStats (versions 2.0 and 4.2). Flowcharts were created using Draw.io (version V24.2.5) (Figure 1). All analyses were weighted according to NHANES guidelines to ensure national representativeness. Initially, participants were grouped by OSA status, and weighted chi-square tests were performed for categorical variables, while weighted Student's t-tests were used for continuous variables to assess differences between groups. Weighted univariate and multivariate logistic regression analyses were then conducted to evaluate the association between NHHR and OSA across different models. Three hierarchical models were applied: the crude model (unadjusted), Model 1 (adjusted for age, sex, and race/ethnicity), and Model 2 (further adjusted for BMI, waist circumference, education level, alcohol consumption, marital status, household poverty-to-income ratio [PIR], hypertension, smoking status, diabetes, sleep duration, and monthly frequency of sleepiness). The hierarchical structure was designed to progressively account for potential confounding factors. The crude model examined the unadjusted association between NHHR and OSA; Model 1 accounted for key demographic differences; and Model 2 incorporated additional lifestyle, metabolic, and socioeconomic variables to more comprehensively isolate the independent effect of NHHR on OSA risk. *P*-values for trends were derived from logistic regression models. Interaction and subgroup analyses were conducted to explore potential effect modifications by gender, age, waist circumference, race/ethnicity, BMI, educational level, and PIR. Furthermore, the dose-response relationship between NHHR and OSA was assessed using smooth curve fitting and threshold effect analyses. The presence of linear or nonlinear relationships was evaluated using log-likelihood ratio tests. Statistical significance was defined as a two-sided *p*-value of less than 0.05.

## 3. Result

### 3.1. Participants' Baseline Characteristics

This study's final analysis encompassed a cohort of 5113 participants, as shown in Table 1. Of these, 2519 were included in the OSA group, with a prevalence of OSA of 49.27% of the total, and the NHHR in this group was 2.98 (2.88 - 3.07), which was statistically significant when compared to that of the patients without OSA [2.57 (2.48 - 2.67), (*p* < 0.001)]. Participants were 48.62% male and 51.38% female. Participants in the OSA group and those in the non-OSA group showed notable differences in terms of gender, age, marital status, BMI, WALST, hypertension (HBP), diabetes, HDL-C, TC, monthly frequency of sleepiness, and smoking. In addition, according to Table 1, those diagnosed with OSA were more likely to be male, married or living with a partner, non-HBP or non-diabetic, sleep 7 - 9 hours per day, obese, and to be non-smokers and sleepy 2 - 4 times per month.

**Table 1.** Overall participant characteristics based on whether obstructive sleep apnea (OSA) was categorized by NHANES, 2015-2018 (N = 5113).

Characteristics	Total (N = 5113)	Obstructive Sleep Apnea (OSA)		p-value
		No (N = 2594)	Yes (N = 2519)	
<b>NHHR</b>	2.76 (2.67 - 2.86)	2.57 (2.48 - 2.67)	2.98 (2.88 - 3.07)	<0.0001
<b>Age (years)</b>	47.66 (46.43 - 48.88)	45.26 (43.88 - 46.64)	50.30 (48.97 - 51.63)	<0.0001
<b>WAIST</b>	100.53 (99.11 - 101.94)	95.91 (94.25 - 97.58)	105.61 (104.41 - 106.81)	<0.0001
<b>HDL-C (mmol/L)</b>	53.49 (52.54 - 54.44)	55.73 (54.55 - 56.91)	51.02 (50.21 - 51.83)	<0.0001
<b>TC (mmol/L)</b>	187.91 (184.55 - 191.27)	185.97 (182.40 - 189.54)	190.04 (186.29 - 193.79)	0.0228
<b>SEX</b>				0.0017
Male	2486 (48.62%)	1157 (44.60%)	1329 (52.76%)	
Female	2627(51.38%)	1437 (55.40%)	1190 (47.24%)	
<b>Race/Ethnicity</b>				0.6204
Mexican American	718 (14.04%)	348 (13.42%)	370 (14.69%)	
Other Hispanic	486 (9.51%)	237 (9.14%)	249 (9.88%)	
Non-Hispanic white	1789 (34.99%)	914 (35.24%)	875 (34.74%)	
Non-Hispanic black	1138 (22.26%)	573 (22.09%)	565 (22.43%)	
Other Race	982 (19.21%)	522 (20.12%)	460 (18.26%)	
<b>Diabetes</b>				<0.0001
Yes	791 (15.47%)	321 (12.37%)	470 (18.66%)	
No	4159 (81.34%)	2194 (84.58%)	1965 (78.01%)	
Borderline	160 (3.13%)	77 (2.97%)	83 (3.29%)	
Don't Know	3 (0.06%)	2 (0.08%)	1 (0.04%)	
<b>Hypertension</b>				<0.0001
Yes	1892 (37.00%)	797 (30.72%)	1095 (43.47%)	
No	3211 (62.80%)	1791 (69.04%)	1420 (56.37%)	
Don't Know	10 (0.20%)	6 (0.23%)	4 (0.16%)	
<b>Smoking</b>				<0.0001
Yes	2086 (40.80%)	965 (37.20%)	1121 (44.50%)	
No	3027 (59.20%)	1629 (62.80%)	1398 (55.50%)	
<b>Education Level</b>				0.2442
Below high school	968 (19.86%)	470 (19.45%)	498 (20.27%)	
High school	1162 (23.84%)	566 (23.42%)	596 (24.26%)	
College or above	2735 (56.11%)	1375 (56.89%)	1360 (55.35%)	
Refused	2 (0.04%)	2 (0.08%)	0 (0.00%)	
Don't Know	7 (0.14%)	4 (0.17%)	3 (0.12%)	
<b>Marital status</b>				<0.0001
Never married	870 (17.85%)	532 (22.01%)	338 (13.76%)	
Married/Living with a partner	2867 (58.82%)	1294 (53.54%)	1573 (64.02%)	
Widowed/Divorced/Separated	1132 (23.23%)	587 (24.29%)	545 (22.18%)	
Refused	5 (0.10%)	4 (0.17%)	1 (0.04%)	

## Continued

<b>Family PIR</b>				0.4612
<1.45	1471 (32.98%)	752 (33.50%)	719 (32.46%)	
1.46 - 3.23	1495 (33.52%)	736 (32.78%)	759 (34.27%)	
3.25 - 5	1494 (33.50%)	757 (33.72%)	737 (33.27%)	
<b>Alcohol usage</b>				0.2485
Never last year	991 (23.18%)	497 (23.60%)	494 (22.78%)	
At least twice a week	841 (19.67%)	404 (19.18%)	437 (20.15%)	
At least once a week or less	2441 (57.10%)	1204 (57.17%)	1237 (57.03%)	
Refused	1 (0.02%)	0 (0.00%)	1 (0.05%)	
Don't know	1 (0.02%)	1 (0.05%)	0 (0.00%)	
<b>Sleep duration(h/d)</b>				0.2844
<7	1296 (25.54%)	650 (25.28%)	646 (25.80%)	
7 - 9	2566 (50.56%)	1282 (49.86%)	1284 (51.28%)	
>9	1213 (23.90%)	639 (24.85%)	574 (22.92%)	
<b>Monthly frequency of sleepiness</b>				<0.0001
Never	838 (16.39%)	498 (19.20%)	340 (13.50%)	
Rarely—1 time a month	1210 (23.67%)	706 (27.22%)	504 (20.01%)	
Sometimes—2 - 4 times a month	1735 (33.93%)	887 (34.19%)	848 (33.66%)	
Often—5 - 15 times a month	890 (17.41%)	434 (16.73%)	456 (18.10%)	
Almost always—16 - 30 times a month	437 (8.55%)	69 (2.66%)	368 (14.61%)	
Don't know	3 (0.06%)	0 (0.00%)	3 (0.12%)	
<b>BMI</b>				<0.0001
<25	1346 (26.76%)	902 (35.39%)	444 (17.90%)	
[25 - 30)	1599 (31.79%)	821 (32.21%)	778 (31.36%)	
[30 - 40)	1639 (32.58%)	691 (27.11%)	948 (38.21%)	
≥40	446 (8.87%)	135 (5.30%)	311 (12.54%)	

HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; PIR, household poverty-to-income ratio; BMI, body mass index; WAIST, waist circumference; NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OSA, obstructive sleep apnea.

### 3.2. The Possible Connection between OSA and NHHR

As shown in **Table 2**, the results of univariate analysis showed that NHHR, age, being sleepy at least 5 times per month, marital status, BMI, WAIST, and total cholesterol (TC) were positively associated with OSA ( $p < 0.05$ ). In contrast, female, HDL-C, non-hypertensive, non-diabetic, and non-smoking participants were negatively associated with OSA ( $p < 0.05$ ).

A significant association between exposure and outcome variables was identified in the multivariate logistic regression analysis results, and this relationship persisted even after controlling for confounders ( $p$ -value  $< 0.05$ ). **Table 3** displays the multivariate regression analysis's findings. In corrected model 2, the NHHR levels, when evaluated as a continuous variable, exhibited a significant correlation with the incidence of OSA (OR = 1.07, 95% CI: 1.01 - 1.13,  $p = 0.0188$ ). As a cat-

egorical variable (divided into tertiles), as compared to the lowest tertile in corrected model 2, the highest tertile of NHHR was likewise positively correlated with OSA (OR = 1.45, 95% CI: 1.20 - 1.76,  $p = 0.0001$ ). In adjusted Model 2, the  $p$ -value for the trend across tertiles was less than 0.0001.

In addition, a nonlinear relationship between NHHR and OSA risk was observed by smooth curve fitting after adjusting for variables such as age, gender, race/ethnicity, BMI, WAIST, marital status, education level, household PIR, smoking status, diabetes, alcohol usage, hypertension, monthly frequency of sleepiness, and sleep duration (Figure 2). The solid red line shows the fitted relationship between the variables. The 95% fit confidence interval is displayed by the blue bar. Based on the curve analysis of the saturation effect, the data indicated an inflection point of 3.65. When the NHHR value was greater than this point, there was no significant correlation between OSA and NHHR ( $p = 0.2043$ ); however, if the value was less than this point, there was a significant increase in the risk of OSA ( $p < 0.0001$ ) (Table 4).

**Table 2.** Univariate logistic regression analysis of various variables.

Outcome: OSA recoded	OR (95%CI)	$p$ -value
<b>NHHR</b>	1.28 (1.19, 1.37)	<0.0001
<b>Sex (versus Male)</b>		
Female	0.71 (0.57, 0.88)	0.0073
<b>Age (years)</b>	1.02 (1.01, 1.02)	<0.0001
<b>Race/Ethnicity (versus Mexican American)</b>		
Other Hispanic	0.80 (0.53, 1.21)	0.3131
Non-Hispanic white	0.89 (0.69, 1.14)	0.3818
Non-Hispanic black	0.97 (0.71, 1.32)	0.8352
Other Race	0.80 (0.52, 1.22)	0.3209
<b>Hypertension (versus Yes)</b>		
No	0.50 (0.43, 0.59)	<0.0001
Don't Know	0.27 (0.05, 1.41)	0.1437
<b>Diabetes (versus Yes)</b>		
No	0.57 (0.47, 0.71)	0.0002
Borderline	0.89 (0.56, 1.44)	0.6564
Don't Know	0.11 (0.01, 1.20)	0.0946
<b>Smoking (versus Yes)</b>		
No	0.70 (0.61, 0.81)	0.0003
<b>WAIST</b>	1.04 (1.03, 1.04)	<0.0001
<b>Monthly frequency of sleepiness (versus Never)</b>		
Rarely—1 time a month	1.06 (0.77, 1.44)	0.7425
Sometimes—2 - 4 times a month	1.33 (1.02, 1.75)	0.0633
Often—5 - 15 times a month	1.57 (1.08, 2.26)	0.0380
Almost always—16 - 30 times a month	8.40 (5.35, 13.19)	<0.0001

**Continued**

<b>Education Level (versus Below high school)</b>		
High school	0.95 (0.74, 1.22)	0.7067
College or above	0.83 (0.64, 1.07)	0.1690
Don't Know	0.34 (0.10, 1.12)	0.1034
<b>Marital status (versus Never married)</b>		
Married/Living with partner	2.04 (1.53, 2.72)	0.0004
Widowed/Divorced/Separated	1.65 (1.26, 2.16)	0.0032
Refused	0.24 (0.03, 2.20)	0.2298
<b>Family PIR (versus &lt; 1.45)</b>		
1.46 - 3.23	1.12 (0.90, 1.39)	0.3357
3.25 - 5	0.96 (0.73, 1.25)	0.7514
<b>Alcohol usage (versus Never last year)</b>		
At least twice a week	0.93 (0.72, 1.19)	0.5791
At least once a week or less	0.80 (0.61, 1.03)	0.1155
<b>Sleep duration(h/d) (versus &lt; 7)</b>		
7 - 9	0.87 (0.71, 1.07)	0.2147
>9	0.86 (0.68, 1.10)	0.2504
<b>BMI (versus &lt; 25)</b>		
[25 - 30)	2.08 (1.56, 2.77)	0.0003
[30 - 40)	3.33 (2.40, 4.62)	<0.0001
≥40	4.84 (3.38, 6.94)	<0.0001
<b>HDL-C (mmol/L)</b>	0.98 (0.97, 0.98)	<0.0001
<b>TC (mmol/L)</b>	1.00 (1.00, 1.00)	0.0281

HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; PIR, household poverty-to-income ratio; BMI, body mass index; WAIST, waist circumference; NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OSA, obstructive sleep apnea; OR, odds ratio; CI, confidence interval.

**Table 3.** The relationship between OSA and NHHR was analyzed by multivariate logistic regression.

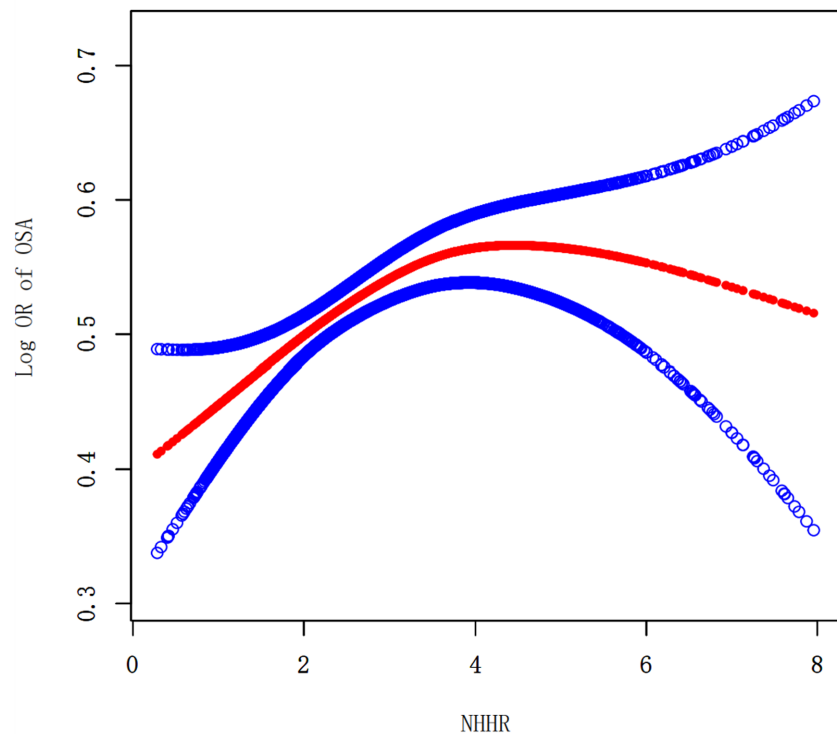
<b>Exposure</b>	<b>Crude model</b>		<b>Model 1</b>		<b>Model 2</b>	
	<b>OR (95%CI)</b>	<b>p-value</b>	<b>OR (95%CI)</b>	<b>p-value</b>	<b>OR (95%CI)</b>	<b>p-value</b>
<b>NHHR continuous</b>	1.22 (1.17, 1.28)	<0.0001	1.21 (1.15, 1.26)	<0.0001	1.07 (1.01, 1.13)	0.0188
<b>NHHR categories</b>						
T1 (0.284 - 2.065)	1.0		1.0		1.0	
T2 (2.067 - 3.079)	1.42 (1.24, 1.62)	<0.0001	1.39 (1.21, 1.60)	<0.0001	1.19 (0.99, 1.43)	0.0599
T3 (3.080 - 27.000)	2.07 (1.81, 2.38)	<0.0001	2.00 (1.73, 2.30)	<0.0001	1.45 (1.20, 1.76)	0.0001
<i>p</i> for trend	1.37 (1.29, 1.46)	<0.0001	1.35 (1.27, 1.44)	<0.0001	1.18 (1.08, 1.28)	0.0001

Crude model: NHHR (non-HDL cholesterol to HDL cholesterol ratio). Model 1: NHHR, age, sex, race/ethnicity. Model 2: NHHR, age, sex, race/ethnicity, BMI (body mass index), WAIST (waist circumference), marital status, education level, household PIR (poverty-to-income ratio), smoking status, diabetes, alcohol usage, hypertension, monthly frequency of sleepiness, sleep duration. OR: odds ratio, CI: confidence interval.

**Table 4.** Saturation effect analysis before and after adjustment of the effect modifier.

		After adjustment	
		OR (95%CI)	<i>p</i> -value
<b>Model I</b>	OR value	1.07 (1.01, 1.13)	0.0188
<b>Model II</b>	Breakpoint (K)	3.65	
	OR1 (<3.65)	1.23 (1.12, 1.36)	<0.0001
	OR2 (>3.65)	0.94 (0.86, 1.03)	0.2043
	OR2/OR1	0.76 (0.65, 0.89)	0.0008
	LRT test		<0.001

Data are presented as OR (95% CI) *p*-values; model I, linear analysis; model II, nonlinear analysis. LRT test, log-likelihood ratio test (*p*-value < 0.05 indicates that model II is significantly different from model I, indicating a nonlinear relationship). OSA: obstructive sleep apnea; NHHR, non-HDL cholesterol to HDL cholesterol ratio; NHANES: National Health and Nutrition Examination Survey.



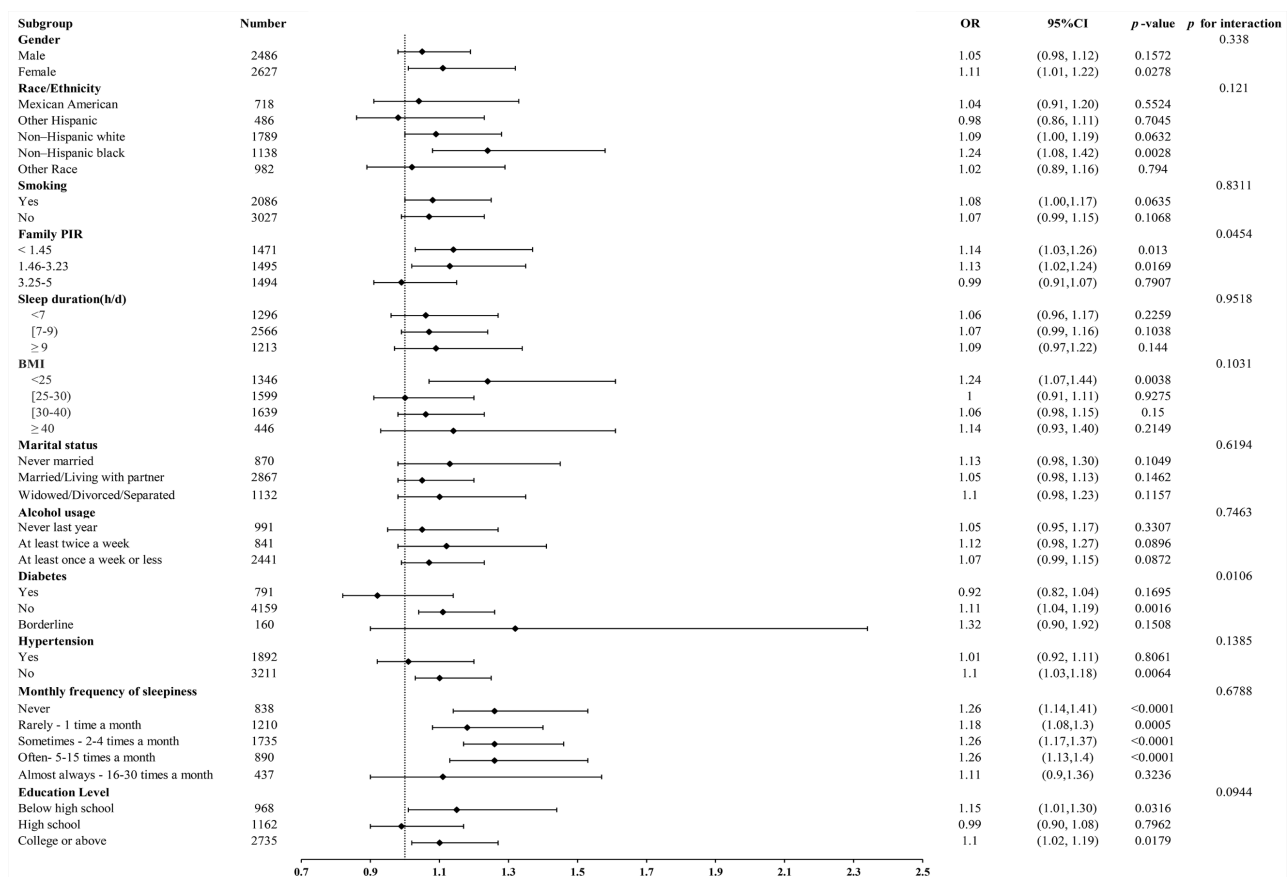
After adjusting for age, gender, race/ethnicity, BMI (body mass index), WAIST (waist circumference), marital status, education level, household PIR (poverty-to-income ratio), smoking status, diabetes, alcohol usage, hypertension, monthly frequency of sleepiness, and sleep duration, a nonlinear relationship was detected.

**Figure 2.** Nonlinear relationship between NHHR and OSA risk.

### 3.3. Subgroup Analysis

As shown in **Figure 3**, subgroup analyses stratified by various variables were conducted to assess the association between NHHR and OSA in different subgroups. This study found that for females (OR = 1.11, 95%CI: 1.01 - 1.22, *p* = 0.0278), from non-Hispanic blacks (OR = 1.24, 95%CI: 1.08 - 1.42, *p* = 0.0028), income

poverty ratios ranged from less than 1.45 (OR = 1.14, 95%CI: 1.03 - 1.26,  $p = 0.0130$ ) or 1.46 - 3.23 (OR = 1.13, 95%CI: 1.02 - 1.24,  $p = 0.0169$ ), a body mass index BMI of less than 25 (OR = 1.24, 95%CI: 1.07 - 1.44,  $p = 0.0038$ ), non-diabetic (OR = 1.11, 95%CI: 1.04 - 1.19,  $p = 0.0016$ ), and non-hypertensive (OR = 1.10, 95% CI: 1.03 - 1.18,  $p = 0.0064$ ) subjects, among others (see **Figure 3** for specific data), the association between NHHR and OSA remained significant. However, subgroup analyses stratified by smoking status, sleep duration, alcohol consumption, and marital status did not support this association. In addition, except for a significant interaction between household poverty-to-income ratio PIR and history of diabetes and NHHR ( $p < 0.05$  for interaction), the associations of the other strata with the prevalence of OSA were not significantly different. These findings imply that the positive association of NHHR with OSA risk was consistent across alcohol consumption, marital status, age, gender, race, education level, BMI, monthly frequency of sleepiness, sleep duration, smoking status, and hypertension ( $p > 0.05$  for all interactions), suggesting that these findings may apply to different population settings.



Adjusted for age, sex, race/ethnicity, BMI (body mass index), marital status, education level, household PIR, smoking status, diabetes, alcohol usage, hypertension, Monthly frequency of sleepiness, and sleep duration. OSA: obstructive sleep apnea; PIR: household poverty-to-income ratio; BMI (body mass index); NHHR, non-high-density lipoprotein cholesterol to HDL cholesterol ratio; CI: confidence interval OR: odds ratio.

**Figure 3.** Subgroup analysis of the association between NHHR and OSA.

## 4. Discussion

In this cross-sectional study involving 5113 participants, we observed a significant and independent positive association between NHHR and the prevalence of obstructive sleep apnea (OSA). Importantly, this relationship persisted after adjustment for a wide range of potential confounders, suggesting that NHHR may serve as a promising biomarker for identifying individuals at higher risk of OSA. The association remained robust across multiple subgroup and interaction analyses, including among non-Hispanic Black participants, females, individuals with a poverty-to-income ratio (PIR) below 3.23, those with a BMI less than 25, and participants without a history of hypertension or diabetes. These findings suggest that the relationship between NHHR and OSA is relatively consistent across various demographic and metabolic contexts. Notably, significant interactions were identified between PIR, diabetes status, and NHHR in relation to OSA risk. Socioeconomic factors, as reflected by PIR, may influence health behaviors, healthcare accessibility, and baseline metabolic risk, thereby modifying the NHHR-OSA association. Diabetes, characterized by chronic inflammation and dyslipidemia, could synergistically interact with elevated NHHR to exacerbate OSA risk. These results emphasize the importance of incorporating metabolic and socioeconomic factors into OSA risk stratification and prevention strategies. Furthermore, smoothed curve fitting and threshold effect analyses revealed a nonlinear relationship, with an inflection point at an NHHR value of 3.65. Below this threshold, higher NHHR was significantly associated with an increased risk of OSA, whereas above this point, the association plateaued and was no longer statistically significant ( $p = 0.2043$ ). This suggests a possible saturation phenomenon in lipid-related pathways, where further increases in NHHR do not confer additional OSA risk due to ceiling effects in inflammatory or oxidative stress mechanisms. Clinically, this implies that moderate elevations in NHHR may warrant heightened surveillance for OSA, while extremely high levels might not further increase risk.

The NHHR is a novel composite index that has recently been developed and used to assess aspects of atherosclerosis extent [32], far surpassing traditional lipid parameters [48]. A growing body of evidence recognizes the NHHR as an accurate indicator of the risk of lipid-related diseases, with greater predictive power for non-alcoholic-fatty-liver-disease (NAFLD) compared to other lipid indicators [36] [49], and as a reliable diagnostic tool for the assessment of insulin resistance and the metabolic syndrome [35], while at the same time, the metric has demonstrated greater predictive accuracy [32]. Several cross-sectional studies have demonstrated significant independent associations between NHHR and diseases such as periodontitis, kidney stones, and depression [34] [38] [39] [50]. In conclusion, NHHR, as a widely used test, shows great promise for clinical implementation due to its noninvasive, easily accessible, and cost-effective nature.

Although the role of NHHR in OSA has not been previously explored, existing literature has documented significant disruptions in lipid metabolism among individuals with OSA. Patients with OSA often exhibit decreased levels of high-den-

sity lipoprotein cholesterol (HDL-C) alongside elevated total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), indicating a pronounced dyslipidemic profile [51]-[53]. In addition, non-traditional lipid indices such as the TG/HDL-C ratio, TC/HDL-C ratio, LDL-C/HDL-C ratio, and non-HDL cholesterol (NHDLC) have been positively correlated with OSA severity [54]. These alterations may be driven by intermittent hypoxia, oxidative stress, and systemic inflammation inherent in OSA. Conversely, dyslipidemia—particularly elevated non-HDL cholesterol—can promote endothelial dysfunction and upper airway collapsibility, potentially exacerbating OSA. NHHR, as a composite index reflecting both atherogenic (non-HDL) and protective (HDL) lipid components, may capture the bidirectional interactions between lipid metabolism and OSA pathophysiology. Supporting this, previous studies have proposed that OSA-induced hypoxia and sleep fragmentation can worsen lipid profiles, while dyslipidemia itself may contribute to the development and progression of OSA [51] [55]-[57]. Therefore, future longitudinal and mechanistic studies are warranted to investigate the causal pathways linking NHHR and OSA.

From a clinical perspective, NHHR could serve as a readily available biomarker to facilitate early OSA risk assessment, particularly in primary care settings where polysomnography resources are limited. Incorporating NHHR into routine lipid screening may help identify individuals at higher risk of OSA, enabling timely referral for diagnostic evaluation and intervention. This approach supports personalized treatment strategies and proactive disease management, potentially reducing the burden of OSA-related complications.

The data for this study came from the NHANES database, which represents the civilian and non-institutionalized national population, making our results more representative and convincing. Also, we analyzed different types of variables and adjusted for covariates to ensure the credibility and generalizability of our findings. However, there are some limitations of this study. First, the self-reports of the participants were used to identify OSA, which raised the likelihood of interviewer bias, recording errors, and recall bias. Second, the cholesterol data analyzed in this study were fasting measurements, while non-fasting data were not examined, potentially introducing bias due to laboratory testing variations. Third, although multiple confounders were considered, influenced by the 2015-2018 NHANES database, we still could not exclude the effect of all potential confounders, and the results may have some bias. Lastly, given that this study draws from cross-sectional data, we must acknowledge the potential for selection bias. This inherent limitation complicates the task of ascertaining a direct cause-and-effect link between the non-HDL to HDL ratio (NHHR) and obstructive sleep apnea (OSA). Therefore, larger-scale prospective cohort studies are needed to test the clinical value of the NHHR marker as a prognostic tool for assessing the progression of OSA.

## 5. Conclusion

In conclusion, the current study demonstrated that there is a non-linear and in-

dependent correlation between NHHR and OSA. This implies that NHHR may be a new biomarker for OSA incidence, which could help with personalized treatment and clinical decision-making. Nevertheless, extensive prospective studies are required to confirm the validity of NHHR as a prognostic marker.

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### **Ethics Statement**

The survey protocol for the NHANES was approved by the CDC's National Center for Health Statistics Institutional Research Ethics Review Board (<https://www.cdc.gov/nchs/nhanes/irba98.htm>).

### **Data Availability**

The datasets generated during and/or analyzed during the current study are publicly available and can be found at <https://www.cdc.gov/nchs/nhanes/index.htm>.

### **Consent for Publication**

This manuscript has been read by all authors who have confirmed their consent for publication.

### **Consent to Participate**

This study used participant data from the NHANES public database; thus, participant statements were unavailable.

### **Author Contributions**

Data curation: Meiyang Rong; Formal analysis: Jiangling Sun; Investigation: Meiyang Rong; Methodology: Jiangling Sun, Cheng Niu; Project administration: Xubo Duan; Software: Zhengfen Li; Writing-original draft: Meiyang Rong; Writing-review & editing: Wei Yang.

### **Conflicts of Interest**

The authors of this work have nothing to disclose.

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## Abbreviations

OSA	Obstructive sleep apnea
PIR	Household poverty-to-income ratio
BMI	Body mass index
WAIST	Waist circumference
HDL-C	High-density lipoprotein
NHHR	Non-high-density lipoprotein cholesterol to HDL cholesterol ratio
NHANES	National health and nutrition examination survey
CI	Confidence interval
OR	Odds ratio