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Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio and incident cardiovascular disease in obstructive sleep apnea: a prospective analysis of the Sleep Heart Health Study

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Research Article

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Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio and incident cardiovascular disease in obstructive sleep apnea: a prospective analysis of the Sleep Heart Health Study

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Abstract

Background

Dyslipidemia is common in obstructive sleep apnea (OSA) and may contribute to its cardiovascular complications. The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) reflects the balance between atherogenic and anti-atherogenic cholesterol. However, its association with long-term cardiovascular risk in individuals with OSA remains unclear. We investigated the association between NHHR and incident cardiovascular disease (CVD) in adults with OSA.

Methods

This prospective analysis included 1,512 adults with OSA from the Sleep Heart Health Study. NHHR was analyzed continuously and by quartiles. Cox proportional hazards models were used to examine the association between NHHR and incident CVD, and restricted cubic splines were used to assess the dose-response relationship. Subgroup analyses were performed according to OSA severity and major metabolic characteristics. NHHR was also compared with the atherogenic index of plasma, lipid accumulation product, visceral adiposity index, and cardiometabolic index.

Results

During a median follow-up of 11.37 years, 344 participants developed incident CVD. After multivariable adjustment, each 1-standard deviation increase in NHHR was associated with a 26% higher risk of CVD (HR 1.26, 95% CI 1.12–1.41; P<0.001). Participants in the highest NHHR quartile had a 55% higher risk than those in the lowest quartile (HR 1.55, 95% CI 1.12–2.13; P=0.008). The association between NHHR and CVD was approximately linear (P overall=0.001; P nonlinear=0.445). The association was stronger in participants with severe OSA (HR per 1-SD 1.49, 95% CI 1.12–1.98), although the interaction across OSA severity was not significant. Stronger associations were also observed among participants with obesity and diabetes. Among the five lipid- and adiposity-related indices examined, NHHR showed the largest numerical improvement in model discrimination when added to conventional clinical factors.

Conclusions

Higher NHHR was associated with an increased long-term risk of incident CVD in adults with OSA. The association was more evident in participants with obesity or diabetes. As a simple index derived from routine lipid measurements, NHHR may provide additional information for cardiovascular risk assessment in OSA, particularly in individuals with accompanying metabolic abnormalities.

Keywords: NHHR; obstructive sleep apnea; cardiovascular disease; non-HDL cholesterol; dyslipidemia;

Background

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder and is closely associated with cardiovascular disease (CVD). Repeated upper-airway obstruction during sleep results in intermittent hypoxemia, sympathetic activation, oxidative stress, and sleep fragmentation, which may contribute to cardiovascular injury[1]. However, cardiovascular outcomes vary considerably among patients with OSA. Increasing evidence suggests that the apnea-hypopnea index (AHI) alone may not fully explain this variability in cardiovascular risk[2]. In addition, OSA frequently coexists with obesity, insulin resistance, dyslipidemia, and other metabolic abnormalities that may further increase cardiovascular risk. Therefore, additional markers reflecting the metabolic risk of patients with OSA may be useful for cardiovascular risk assessment.

Abnormal lipid metabolism may be an important link between OSA and cardiovascular disease. Intermittent hypoxia can disrupt lipid synthesis and clearance, thereby enhancing the oxidative modification of lipoproteins[3]. In addition to conventional lipid measurements, several composite lipid-related indices have been studied in patients with OSA. A previous systematic review and meta-analysis showed that the atherogenic index of plasma (AIP), visceral adiposity index (VAI), and lipid accumulation product (LAP) were higher in individuals with OSA[4]. Genetic evidence has also suggested that lipid-related pathways may be associated with insulin resistance, metabolic syndrome, and cardiovascular risk in individuals with OSA[5]. These findings suggest that lipid-related indices may provide useful information on the metabolic abnormalities accompanying OSA.

The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) is calculated based on routine lipid parameters. Non-HDL cholesterol encompasses cholesterol carried by multiple atherogenic lipoproteins, whereas HDL cholesterol is commonly considered to exerts an anti-atherogenic role. Thus, NHHR may provide a simple measure of the balance between these two lipid components. Recent studies have linked elevated NHHR to various cardiometabolic outcomes. In a cross-sectional study based on the National Health and Nutrition Examination Survey, higher NHHR was associated with OSA[6]. A prospective study from the China Health and Retirement Longitudinal Study further revealed that baseline and cumulative NHHR were associated with incident CVD[7]. A recent prospective cohort study found that a higher remnant cholesterol-to-HDL-C ratio was associated with an increased risk of incident atherosclerotic CVD[8]. However, evidence regarding the long-term cardiovascular significance of NHHR specifically among patients with OSA remains limited.

Therefore, we investigated the prospective association between NHHR and incident CVD among adults with OSA. We analyzed NHHR as both a continuous and categorical variable and assessed its dose-response relationship with CVD. We also explored whether the association differed according to OSA severity and other clinical characteristics. In addition, NHHR was compared with AIP, LAP, VAI, and cardiometabolic index (CMI) to evaluate its relative association with and incremental discrimination for incident CVD. We hypothesized that elevated NHHR would be associated with an higher long-term risk of CVD in adults with OSA.

Methods

Study population

The Sleep Heart Health Study (SHHS) is a multicenter, community-based prospective cohort established to examine the cardiovascular consequences of sleep-disordered breathing. Adults aged 40 years and older were recruited from existing population-based cohorts. At SHHS Visit 1, participants underwent clinical assessment, laboratory testing, and unattended overnight polysomnography[9].

SHHS Visit 1 was defined as the baseline for the present study. Baseline demographic, clinical, laboratory, and polysomnographic data were linked to cardiovascular follow-up data. Participants were included if they had OSA at baseline and had available follow-up information. We excluded participants with prevalent CVD at baseline, including myocardial infarction, stroke, angina, congestive heart failure, or previous coronary revascularization. Participants with missing data for NHHR or variables included in the fully adjusted model were also excluded. Finally, 1,512 participants with OSA were included in the analysis.

The original SHHS was approved by the institutional review boards of the participating centers, and written informed consent was obtained from all participants. The present study used de-identified data available from the National Sleep Research Resource.

Assessment of OSA

Sleep-disordered breathing was assessed by unattended type II polysomnography performed at home. Data acquisition and scoring followed the standardized SHHS protocol[10].Participants with an apnea-hypopnea index (AHI) ≥5 events/h were classified as having OSA. OSA severity was further classified as mild (AHI 5 to <15 events/h), moderate (15 to <30 events/h), or severe (≥30 events/h).

NHHR and other cardiometabolic indices

Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured at SHHS Visit 1. Non-HDL-C was calculated by subtracting HDL-C from TC. NHHR was calculated as:NHHR = (TC − HDL-C) / HDL-C.

Four other commonly used lipid- and adiposity-related indices were calculated for comparison with NHHR: the atherogenic index of plasma (AIP), lipid accumulation product (LAP), visceral adiposity index (VAI), and cardiometabolic index (CMI).

AIP was calculated as[11]:AIP = log10 (TG / HDL-C).

LAP was calculated using sex-specific formulas[10]:Men: LAP = (WC − 65) × TG； Women: LAP = (WC − 58) × TG.

VAI was calculated according to previously reported sex-specific formulas[12]:Men: VAI = [WC / (39.68 + 1.88 × BMI)] × (TG / 1.03) × (1.31 / HDL-C)； Women: VAI = [WC / (36.58 + 1.89 × BMI)] × (TG / 0.81) × (1.52 / HDL-C).

CMI was calculated as[13]:CMI = (TG / HDL-C) × (WC / height).

Cardiovascular outcomes

The primary outcome was incident CVD during follow-up. Cardiovascular events were obtained from the surveillance systems of the SHHS parent cohorts and harmonized within the SHHS cardiovascular outcome dataset. The harmonized any_cvd variable, indicating any CVD since baseline polysomnography as recorded in the parent-study datasets, was used as the primary

endpoint.

Participants with prevalent CVD prior to SHHS Visit 1 were excluded. Follow-up time was calculated from the baseline examination to the first recorded CVD event. Participants without incident CVD were censored at their last valid cardiovascular follow-up assessment. Cardiovascular outcomes from the SHHS have been used in previous prospective studies of sleep-disordered breathing and CVD.

Statistical analysis

Baseline characteristics are presented for the overall population and according to NHHR quartiles. Normally distributed continuous variables are expressed as mean ± SD and were compared using Welch's one-way analysis of variance. Variables with skewed distributions are presented as median (interquartile range) and are compared using the Kruskal-Wallis test. Categorical variables are presented as number (percentage) and were compared using Pearson's χ^2 test.

Cox proportional hazards regression models was used to examine the association between NHHR and incident CVD. NHHR was analyzed per 1-SD increase and by quartiles, with the lowest quartile serving as the reference group. Three models were constructed. Model 1 was adjusted for age, sex, and race. Model 2 was additionally adjusted for BMI, smoking status, and alcohol use. Model 3 was further adjusted for diabetes, hypertension, lipid-lowering medication use, and OSA severity.

Adjusted CVD-free survival curves were plotted across NHHR quartiles. Restricted cubic spline analysis based on the fully adjusted Cox model was used to examine the shape of the association between NHHR and CVD. The median NHHR served as the reference. P values for the overall association and nonlinearity were calculated.

Subgroup analyses were performed stratified by OSA severity, sex, age (<65 or ≥65 years), obesity (BMI <30 or ≥30 kg/m²), hypertension, and diabetes. HRs and 95% confidence intervals (CIs) were estimated for each 1-SD increase in NHHR. Interaction terms were incorporated into the Cox models to test whether the association differed across subgroups.

For comparison with other cardiometabolic indices, NHHR, AIP, LAP, VAI, and CMI were standardized and entered separately into the fully adjusted Cox model. Harrell's concordance index (C-index) was calculated for each index. Each index was then added separately to a clinical base model including age, sex, race, BMI, smoking status, alcohol use, diabetes, hypertension, lipid-lowering medication use, and OSA severity. The change in C-index (ΔC-index) was calculated.

Time-dependent receiver-operating characteristic analysis was also conducted for 5-year and 10-year outcomes. The change in area under the curve (ΔAUC) after adding each index to the clinical base model was used to quantify its incremental discriminative ability. Complete cases were used for the main analyses. All tests were two-sided, and $P<0.05$ was considered statistically significant. Statistical analyses were performed using R software.

Results

Baseline characteristics

A total of 1,512 participants with OSA were included. The mean age was 65.6 ± 9.9 years, 865 (57.2%) were men, and the mean BMI was 30.1 ± 5.4 kg/m². Of these participants, 962 (63.6%) had mild OSA, 362 (23.9%) had moderate OSA, and 188 (12.4%) had severe OSA. The median NHHR was 3.36 (interquartile range, 2.53–4.38). During a median follow-up of 11.37 years, 344 participants (22.8%) developed incident CVD **(Table 1)**.

Several baseline characteristics differed across NHHR quartiles. Participants with higher NHHR were younger, more often male, and had higher BMI and waist circumference. AHI also increased across NHHR quartiles. As expected, higher NHHR was accompanied by higher total cholesterol, triglycerides, and non-HDL-C and lower HDL-C (all P<0.001). The proportion of severe OSA increased from 10.8% in Q1 to 16.9% in Q4 (P=0.005). Lipid-lowering medication use increased from 3.7% to 19.0% across the four quartiles (P<0.001). Follow-up duration was similar among the quartiles (P=0.983). The crude incidence of CVD was 22.2%, 19.8%, 22.8%, and 26.2% from Q1 to Q4, respectively (P=0.219).

Association between NHHR and incident CVD

Higher NHHR was associated with incident CVD in the Cox regression analyses **(Table 2)**. In Model 1, adjusted for age, sex, and race, the HR for each 1-SD increase in NHHR was 1.31 (95% CI 1.17–1.45; P<0.001). The association remained after further adjustment for BMI, smoking status, and alcohol use (Model 2: HR 1.26, 95% CI 1.12–1.40; P<0.001). In the fully adjusted model, which additionally included diabetes, hypertension, lipid-lowering medication use, and OSA severity, the HR was 1.26 (95% CI 1.12–1.41; P<0.001).

When NHHR was analyzed by quartiles, participants in Q4 had a higher CVD risk than those in Q1. The HR for Q4 versus Q1 was 1.81 (95% CI 1.33–2.46; P<0.001) in Model 1 and 1.55 (95% CI 1.12–2.13; P=0.008) in Model 3. No significant associations were observed for Q2 (HR 0.81, 95% CI 0.58–1.11; P=0.184) or Q3 (HR 1.16, 95% CI 0.84–1.59; P=0.368) in the fully adjusted model.

The adjusted CVD-free survival curves according to NHHR quartiles are shown in Figure 1. Participants in the highest NHHR quartile had the lowest CVD-free survival during follow-up, and the overall difference among the four groups was significant (P<0.001).

Dose-response association

The restricted cubic spline analysis is shown in **Figure 2**. NHHR was associated with incident CVD in the fully adjusted model (P overall=0.001). There was no evidence of a nonlinear association (P nonlinear=0.445). The estimated HR increased with higher NHHR, particularly above the middle range of the distribution, although the confidence intervals became wider at the highest NHHR values.

Subgroup analyses

Figure 3 shows the association between NHHR and incident CVD in different subgroups. By OSA severity, the HR per 1-SD increase in NHHR was 1.19 (95% CI 1.02–1.38; P=0.029) in mild OSA, 1.23 (95% CI 0.96–1.57; P=0.095) in moderate OSA, and 1.49 (95% CI 1.12–1.98; P=0.007) in severe OSA. The interaction between NHHR and OSA severity was not significant (P for interaction=0.298).

The associations were similar in men and women (P for interaction=0.352) and according to hypertension status (P for interaction=0.403). The association tended to be stronger in participants aged <65 years, although the interaction did not reach statistical significance (P for interaction=0.069).

Differences were observed according to obesity and diabetes status. Among participants with obesity, the HR per 1-SD increase in NHHR was 1.47 (95% CI 1.25–1.72), compared with 1.13 (95% CI 0.96–1.32) among those without obesity (P for interaction=0.041). Among participants with diabetes, the corresponding HR was 1.60 (95% CI 1.22–2.10), compared with 1.23 (95% CI 1.08–1.40) among those without diabetes (P for interaction=0.042).

Comparison with other cardiometabolic indices

The associations of NHHR, AIP, LAP, VAI, and CMI with incident CVD are shown in **Supplementary Table S1**. All five indices were associated with incident CVD after multivariable adjustment. The HRs per 1-SD increase were 1.26 (95% CI 1.12–1.41) for NHHR, 1.25 (95% CI 1.11–1.41) for AIP, 1.15 (95% CI 1.05–1.26) for LAP, 1.12 (95% CI 1.04–1.20) for VAI, and 1.14 (95% CI 1.06–1.22) for CMI.

When each index was added to the clinical base model, the changes in discrimination were small. NHHR showed the largest numerical increase in C-index (ΔC-index=0.0045). The changes in AUC after adding NHHR were 0.0034 at 5 years and 0.0046 at 10 years. The 10-year ΔAUC was numerically higher for NHHR than for the other four indices. The time-dependent ROC curves for the five models largely overlapped **(Supplementary Figure S1).**

Discussion

In this prospective study of adults with OSA, higher NHHR was associated with a higher risk of incident CVD during long-term follow-up. After adjustment for demographic factors, BMI, lifestyle factors, diabetes, hypertension, lipid-lowering medication use, and OSA severity, each 1-SD increment in NHHR was associated with a 26% higher risk of incident CVD. Participants in the highest NHHR quartile also had a 55% higher risk compared with those in the lowest quartile. The restricted cubic spline analysis suggested an approximately linear association. The association was stronger among participants with obesity and diabetes, while the effect estimate was also numerically higher in severe OSA. These findings suggest that NHHR may provide useful information on cardiovascular risk among patients with OSA, especially in the presence of metabolic abnormalities.

Several studies have reported associations between NHHR and cardiovascular outcomes. In adults with diabetes or prediabetes from NHANES, higher NHHR was associated with all-cause and cardiovascular mortality[14]. A recent prospective study based on the China Health and Retirement Longitudinal Study showed that both baseline and cumulative NHHR were associated with incident CVD[7]. In patients undergoing percutaneous coronary intervention, Liu et al. also found that higher NHHR was associated with adverse cardiovascular outcomes[15]. Furthermore, in a prospective cohort with a median follow-up of 27.8 years, Laukkanen et al. reported a positive dose-response association between NHHR and sudden cardiac death[16]. These findings support an association between higher NHHR and cardiovascular risk across different populations. Our study extends this evidence to individuals with objectively assessed OSA and shows that higher NHHR is associated with incident CVD during long-term follow-up.

The relationship between lipid abnormalities and OSA has also received increasing attention. Pan et al. reported a positive association between NHHR and OSA in a cross-sectional analysis of NHANES data[6]. Basoglu et al. found that non-HDL-C was associated with OSA severity and nocturnal hypoxemia, whereas LDL-C was not[17]. Fang et al. also reported positive associations between several nontraditional lipid indices and OSA severity[18]. Genetic evidence has further suggested that lipid-related pathways may be associated with insulin resistance, metabolic syndrome, and cardiovascular risk in individuals with OSA[5]. In addition, Cao et al. found that the coexistence of OSA and dyslipidemia was associated with a higher prevalence of atherosclerotic cardiovascular disease, with the strongest association observed in patients with severe OSA[19]. However, these studies mainly focused on the presence or severity of OSA, or on prevalent cardiovascular disease. Our study extends these findings by showing that, among individuals with objectively assessed OSA, higher NHHR was prospectively associated with incident CVD during long-term follow-up. This finding may be clinically relevant because cardiovascular outcomes vary considerably even among patients with similar levels of sleep-disordered breathing.

We found that the association between NHHR and CVD was numerically strongest in severe OSA, but the interaction according to OSA severity was not statistically significant. One possible explanation is that AHI does not fully reflect the physiological stress caused by OSA. Patients with similar AHI values may have different degrees of nocturnal hypoxemia, sleep fragmentation, and autonomic disturbance. Previous work has shown that polysomnographic phenotypes can identify differences in cardiovascular risk that are not well explained by conventional AHI categories[20]. In addition, sleep apnea-specific hypoxic burden was associated with cardiovascular mortality in both

the Sleep Heart Health Study and the Osteoporotic Fractures in Men Study[21]. Therefore, the absence of a clear interaction by AHI-defined OSA severity does not necessarily mean that OSA-related physiological stress is unimportant. NHHR and AHI may reflect different aspects of cardiovascular risk.

There are several possible mechanisms linking NHHR with cardiovascular disease in OSA. Non-HDL-C includes cholesterol carried by multiple atherogenic lipoproteins, while HDL-C is generally associated with reverse cholesterol transport and other anti-atherogenic functions. A higher NHHR therefore reflects a shift toward a more atherogenic lipid profile. This may be particularly relevant in OSA ,given that intermittent hypoxia can disrupts lipid metabolism. Experimental studies have shown that chronic intermittent hypoxia can inhibit lipoprotein lipase activity through pathways involving hypoxia-inducible factor-1 and angiopoietin-like protein 4, leading to impaired clearance of triglyceride-rich lipoproteins and accelerated atherosclerosis[22]. Intermittent hypoxia may also promote oxidative stress, inflammation, and endothelial dysfunction[3]. In our study, participants with higher NHHR also had higher BMI, waist circumference, triglycerides, and non-HDL-C and lower HDL-C. These findings suggest that NHHR may reflect part of the adverse metabolic background commonly seen in OSA.

The subgroup findings for obesity and diabetes are also of interest. The association between NHHR and CVD was stronger in participants with obesity than in those without obesity, and the interaction was statistically significant. A similar pattern was observed for diabetes. Obesity and diabetes are both associated with insulin resistance, dyslipidemia, inflammation, and increased cardiovascular risk, which may enhance the cardiovascular consequences of an atherogenic lipid profile. Xia et al. previously reported an interaction between obesity and intermittent hypoxia in relation to dyslipidemia in patients evaluated for OSA[23]. In addition, NHHR has been associated with cardiovascular mortality among people with diabetes or prediabetes[14]. Our results therefore suggest that NHHR may be more informative in OSA patients with additional metabolic abnormalities.

We also compared NHHR with AIP, LAP, VAI, and CMI. All five indices were associated with incident CVD after multivariable adjustment. Previous prospective evidence has similarly linked higher LAP with incident CVD[24], and both LAP and CMI have been associated with metabolic syndrome[25]. In our study, AIP had a slightly higher C-index when used alone, whereas NHHR showed the largest numerical increase in C-index after being added to the clinical base model. NHHR also showed the largest numerical improvement in 10-year AUC. NHHR has an important practical advantage, it can be directly calculated from a routine lipid profile without additional anthropometric measurements or laboratory tests, which may make it convenient for clinical risk assessment.

This study has several strengths. OSA was ascertained using unattended overnight polysomnography rather than self-reported symptoms or questionnaires. Participants with prevalent CVD were excluded, and the median follow-up was more than 11 years, allowing us to examine incident cardiovascular events. NHHR was evaluated as both a continuous and categorical variable, and the dose-response relationship was further examined using restricted cubic splines. We also compared NHHR with several other lipid- and adiposity-related indices, providing additional context for its cardiovascular association.

Overall, higher NHHR was associated with an increased long-term risk of incident CVD among adults with OSA, with an approximately linear association that remained after adjustment

for conventional cardiovascular risk factors and OSA severity. As a simple index derived from routine lipid measurements, NHHR may provide additional information for identifying OSA patients at higher cardiovascular risk, particularly those with accompanying obesity or diabetes. These findings also highlight the potential importance of metabolic abnormalities, in addition to conventional OSA severity, in cardiovascular risk assessment. Future studies combining NHHR with measures of nocturnal hypoxemia or hypoxic burden may further clarify whether metabolic and sleep-related information can improve cardiovascular risk stratification in OSA.

Conclusions

Higher NHHR was associated with an increased long-term risk of incident CVD among adults with OSA, independent of conventional cardiovascular risk factors and OSA severity. The association was approximately linear and was more pronounced in participants with obesity or diabetes. As a simple index derived from routine lipid measurements, NHHR may provide additional information for cardiovascular risk assessment in OSA, particularly in patients with accompanying metabolic abnormalities. Further studies incorporating NHHR with measures of nocturnal hypoxemia may help refine cardiovascular risk stratification in this population.

List of abbreviations

AHI, apnea-hypopnea index; AIP, atherogenic index of plasma; AUC, area under the curve; BMI, body mass index; CI, confidence interval; CMI, cardiometabolic index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LAP, lipid accumulation product;NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; NSRR, National Sleep Research Resource; OSA, obstructive sleep apnea; SD, standard deviation; SHHS, Sleep Heart Health Study; TC, total cholesterol; TG, triglycerides; VAI, visceral adiposity index; WC, waist circumference.

Declarations

Ethics approval and consent to participate

The original Sleep Heart Health Study protocols were approved by the institutional review boards of the participating centers, and written informed consent was obtained from all participants. The original study was conducted in accordance with the principles of the Declaration of Helsinki. The present analysis used de-identified data obtained from the National Sleep Research Resource.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available through the National Sleep Research Resource Sleep Heart Health Study repository (https://sleepdata.org/datasets/shhs), subject to the repository's data access requirements.

Competing interests

The authors declare no conflicts of financial interest.

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Authors' contributions

YL conceived the study, performed the data analysis, and drafted the manuscript. WH

contributed to the study conception and obtained access to the study data. YXL contributed to the translation and language editing of the manuscript. WQ critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline and follow-up characteristics of participants with obstructive sleep apnea according to NHHR quartiles

Characteristics	Overall	Q1	Q2	Q3	Q4	P value
Baseline characteristics						
Age, years	65.6 ± 9.9	68.1 ± 9.5	67.0 ± 9.6	64.5 ± 10.0	62.7 ± 9.5	<0.001
Sex						<0.001
Male	865 (57.2%)	150 (39.7%)	201 (53.2%)	244 (64.6%)	270 (71.4%)	
Female	647 (42.8%)	228 (60.3%)	177 (46.8%)	134 (35.4%)	108 (28.6%)	
Race						<0.001
White	1,354 (89.6%)	343 (90.7%)	337 (89.2%)	338 (89.4%)	336 (88.9%)	
Black	85 (5.6%)	27 (7.1%)	28 (7.4%)	21 (5.6%)	9 (2.4%)	
Other	73 (4.8%)	8 (2.1%)	13 (3.4%)	19 (5.0%)	33 (8.7%)	
BMI, kg/m²	30.1 ± 5.4	28.2 ± 5.2	29.9 ± 5.3	30.9 ± 5.5	31.6 ± 5.0	<0.001
Waist circumference, cm	102.6 ± 13.0	96.8 ± 13.6	102.3 ± 12.8	105.4 ± 12.7	105.9 ± 11.0	<0.001
AHI, events/hour	11.6 (7.5, 19.5)	10.7 (7.0, 16.4)	11.2 (7.1, 17.9)	12.0 (8.4, 19.8)	13.1 (7.9, 23.0)	<0.001
OSA severity						0.005
Mild	962 (63.6%)	262 (69.3%)	251 (66.4%)	229 (60.6%)	220 (58.2%)	
Moderate	362 (23.9%)	75 (19.8%)	87 (23.0%)	106 (28.0%)	94 (24.9%)	
Severe	188 (12.4%)	41 (10.8%)	40 (10.6%)	43 (11.4%)	64 (16.9%)	
Smoking status						0.038
Never	701 (46.4%)	202 (53.4%)	178 (47.1%)	160 (42.3%)	161 (42.6%)	
Former	715 (47.3%)	158 (41.8%)	178 (47.1%)	190 (50.3%)	189 (50.0%)	

Characteristics	Overall	Q1	Q2	Q3	Q4	P value
Current	96 (6.3%)	18 (4.8%)	22 (5.8%)	28 (7.4%)	28 (7.4%)	
Alcohol use	650 (43.0%)	183 (48.4%)	157 (41.5%)	167 (44.2%)	143 (37.8%)	0.027
Hypertension	611 (40.4%)	133 (35.2%)	167 (44.2%)	150 (39.7%)	161 (42.6%)	0.062
Diabetes mellitus	121 (8.0%)	19 (5.0%)	33 (8.7%)	35 (9.3%)	34 (9.0%)	0.105
Lipid-lowering medication	166 (11.0%)	14 (3.7%)	35 (9.3%)	45 (11.9%)	72 (19.0%)	<0.001
Total cholesterol, mg/dL	206.2 ± 36.9	189.2 ± 33.0	199.4 ± 30.6	206.6 ± 31.9	229.7 ± 39.1	<0.001
HDL-C, mg/dL	48.7 ± 14.9	65.7 ± 14.9	51.0 ± 8.5	42.9 ± 6.9	35.3 ± 6.6	<0.001
Triglycerides, mg/dL	129.0 (96.0, 186.0)	90.0 (67.0, 117.0)	112.0 (89.0, 142.0)	145.0 (109.0, 193.0)	196.5 (151.0, 267.0)	<0.001
Non-HDL-C, mg/dL	157.5 ± 38.0	123.5 ± 26.3	148.4 ± 23.0	163.7 ± 25.6	194.4 ± 35.6	<0.001
NHHR	3.36 (2.53, 4.38)	2.04 (1.64, 2.30)	2.91 (2.73, 3.13)	3.81 (3.57, 4.07)	5.28 (4.78, 5.97)	<0.001
Follow-up characteristics						
Median follow-up, years	11.37 (8.43, 12.18)	11.34 (8.26, 12.12)	11.41 (8.89, 12.15)	11.38 (8.01, 12.23)	11.25 (8.39, 12.32)	0.983
Incident CVD	344 (22.8%)	84 (22.2%)	75 (19.8%)	86 (22.8%)	99 (26.2%)	0.219

Note. Data are presented as mean ± SD, median (interquartile range), or n (%), as appropriate. P values were calculated using Welch's one-way analysis of variance, Kruskal-Wallis test, or Pearson's χ^2 test, as appropriate.

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OSA, obstructive sleep apnea; SD, standard deviation.

Table 2. Association between NHHR and incident cardiovascular disease among participants with obstructive sleep apnea

	Model 1		Model 2		Model 3	
NHHR	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Per 1-SD increase	1.31 (1.17–1.45)	<0.001	1.26 (1.12–1.40)	<0.001	1.26 (1.12–1.41)	<0.001
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	0.93 (0.68–1.27)	0.655	0.86 (0.63–1.18)	0.351	0.81 (0.58–1.11)	0.184
Q3	1.32 (0.97–1.79)	0.079	1.19 (0.87–1.63)	0.275	1.16 (0.84–1.59)	0.368

	Model 1		Model 2		Model 3	
NHHR	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Q4	1.81 (1.33–2.46)	<0.001	1.58 (1.16–2.17)	0.004	1.55 (1.12–2.13)	0.008

Note. Model 1 was adjusted for age, sex, and race. Model 2 was additionally adjusted for BMI, smoking status, and alcohol use. Model 3 was additionally adjusted for diabetes, hypertension, lipid-lowering medication use, and OSA severity. Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OSA, obstructive sleep apnea; SD, standard deviation.

Supplementary Table S1. Comparative associations and discrimination performance of lipid-related indices for incident cardiovascular disease among participants with obstructive sleep apnea

Indicator	Adjusted HR per 1-SD (95% CI)	P value	C-index alone (95% CI)	ΔC-index	5-year ΔAUC	10-year ΔAUC
NHHR	1.26 (1.12–1.41)	<0.001	0.521 (0.490–0.552)	+0.0045	+0.0034	+0.0046
AIP	1.25 (1.11–1.41)	<0.001	0.539 (0.508–0.569)	+0.0037	+0.0015	+0.0037
LAP	1.15 (1.05–1.26)	0.002	0.515 (0.483–0.546)	+0.0014	+0.0028	+0.0016
VAI	1.12 (1.04–1.20)	0.003	0.528 (0.497–0.558)	+0.0018	+0.0027	+0.0018
CMI	1.14 (1.06–1.22)	<0.001	0.535 (0.504–0.567)	+0.0022	+0.0031	+0.0020

Note. Adjusted HRs represent incident CVD risk per 1-SD increase in each index. Cox models were adjusted for age, sex, race, BMI, smoking status, alcohol use, diabetes, hypertension, lipid-lowering medication use, and OSA severity. C-index alone is Harrell's concordance index from a Cox model containing the individual index as the sole predictor. ΔC-index is the difference between the Clinical Base + index model and the Clinical Base model. ΔAUC is the corresponding difference in time-dependent AUC at 5 and 10 years. Abbreviations: AIP, atherogenic index of plasma; AUC, area under the curve; BMI, body mass index; CMI, cardiometabolic index; CVD, cardiovascular disease; HR, hazard ratio; LAP, lipid accumulation product; NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OSA, obstructive sleep apnea; VAI, visceral adiposity index.

Figure legends and figures

Figure 1. Adjusted CVD-free survival according to NHHR quartiles.

Covariate-adjusted CVD-free survival curves are shown for NHHR quartiles. The model was adjusted for age, sex, race, BMI, smoking status, alcohol use, diabetes, hypertension, lipid-lowering medication use, and OSA severity. Numbers at risk are shown below the plot. Abbreviations: BMI, body mass index; CVD, cardiovascular disease; NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OSA, obstructive sleep apnea.

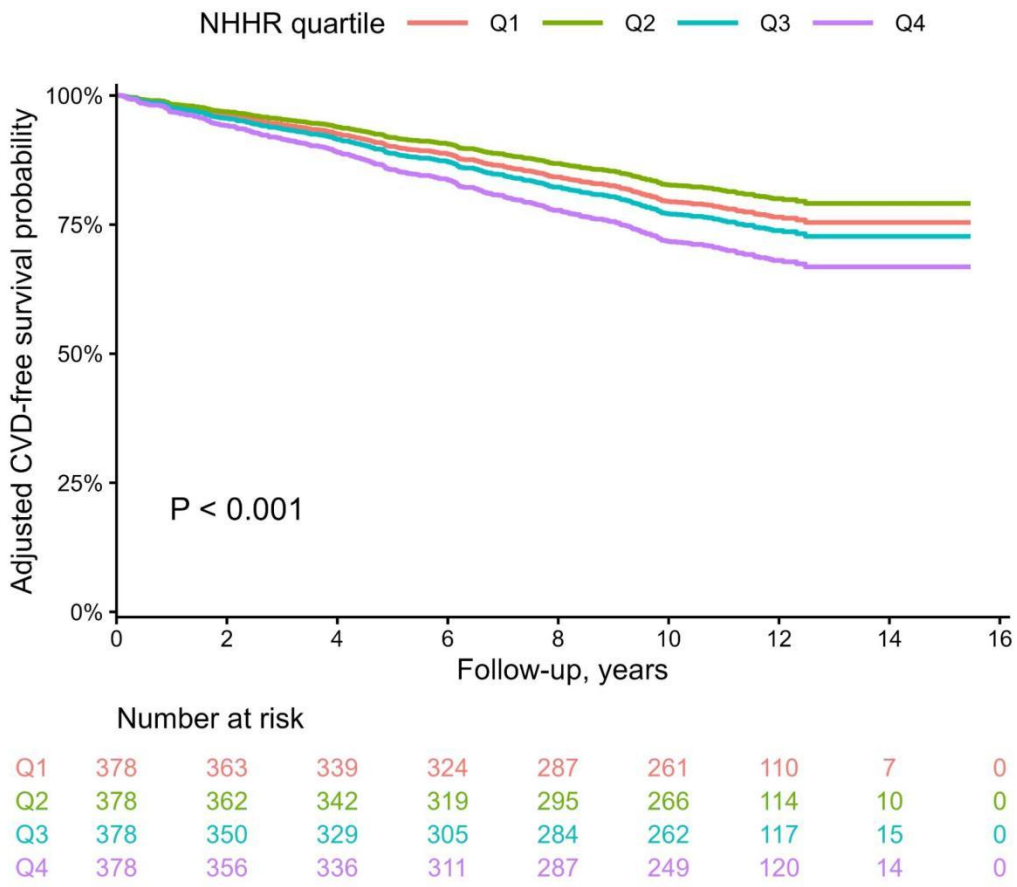


Figure 2. Dose-response association between NHHR and incident CVD.

Restricted cubic spline analysis was based on the fully adjusted Cox model, with the median NHHR used as the reference. The solid line represents the estimated hazard ratio and the shaded area the 95% confidence interval. The horizontal dashed line indicates HR=1. Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio.

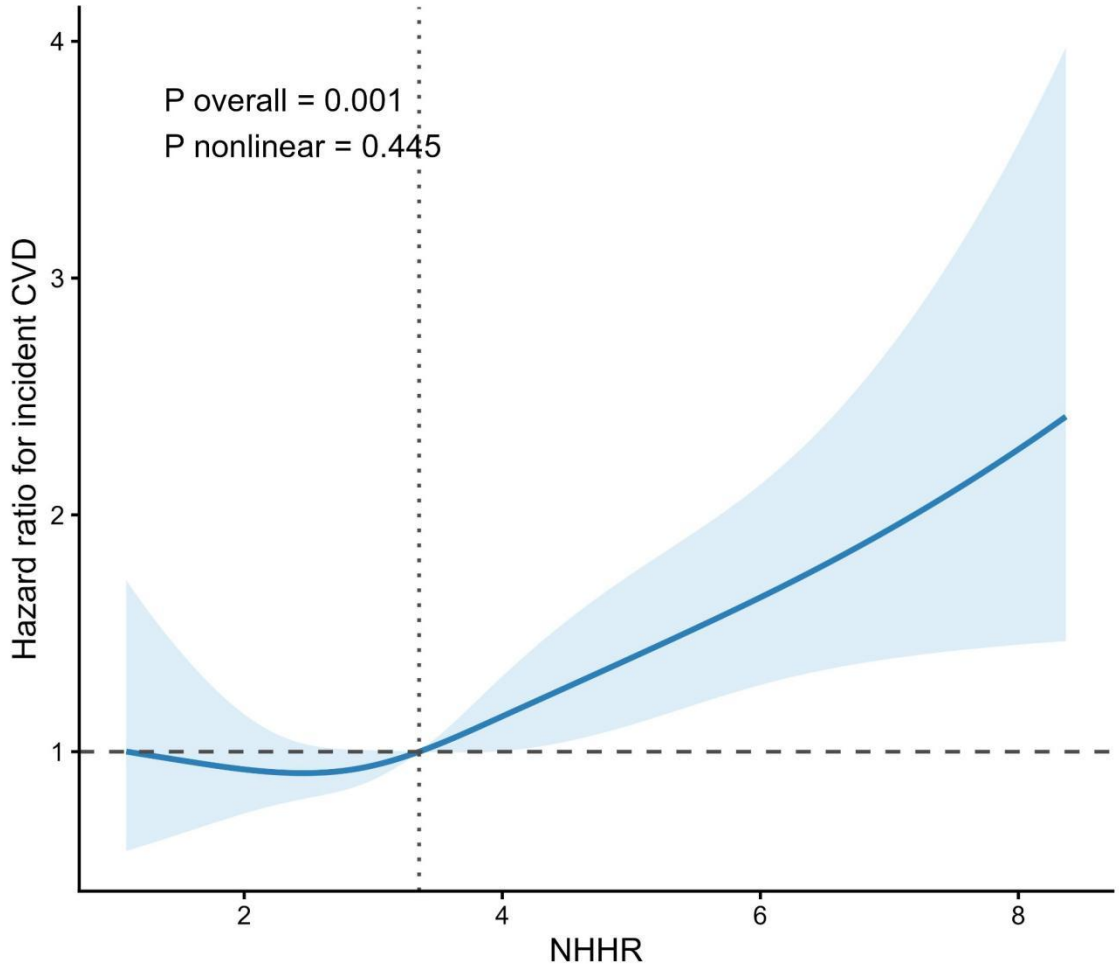
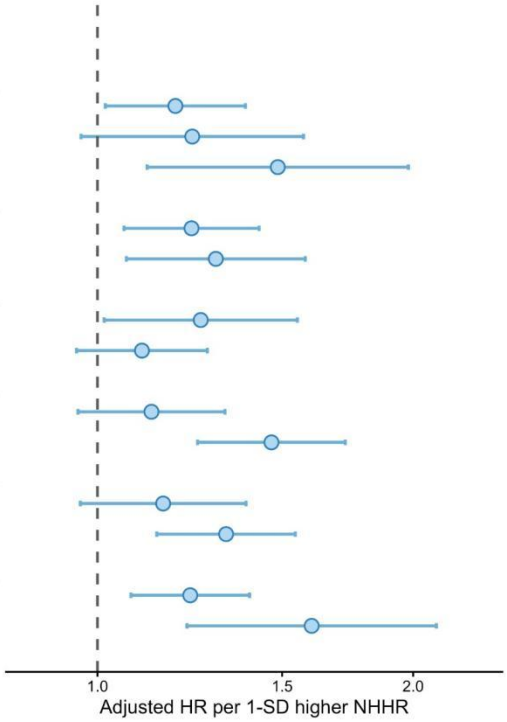


Figure 3. Subgroup analyses of NHHR and incident CVD.

Adjusted hazard ratios and 95% confidence intervals are shown per 1-SD increase in NHHR. P values for interaction assess heterogeneity across each subgroup variable. Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; OSA, obstructive sleep apnea; SD, standard deviation.

Subgroup	HR (95% CI)	P for interaction
OSA severity		0.298
Mild	1.19 (1.02–1.38)	0.029
Moderate	1.23 (0.96–1.57)	0.095
Severe	1.49 (1.12–1.98)	0.007
Sex		0.352
Male	1.23 (1.06–1.43)	0.006
Female	1.30 (1.07–1.58)	0.010
Age		0.069
<65 years	1.25 (1.01–1.55)	0.036
≥65 years	1.10 (0.96–1.27)	0.183
Obesity		0.041
<30 kg/m²	1.13 (0.96–1.32)	0.150
≥30 kg/m²	1.47 (1.25–1.72)	<0.001
Hypertension		0.403
No	1.15 (0.96–1.39)	0.121
Yes	1.33 (1.14–1.54)	<0.001
Diabetes		0.042
No	1.23 (1.08–1.40)	0.002
Yes	1.60 (1.22–2.10)	<0.001



Supplementary Figure S1. Time-dependent ROC curves for 5- and 10-year incident CVD.

The Clinical Base model included age, sex, race, BMI, smoking status, alcohol use, diabetes, hypertension, lipid-lowering medication use, and OSA severity. Each lipid- or adiposity-related index was added separately to the Clinical Base model. AUC values are shown in the figure legend. Abbreviations: AIP, atherogenic index of plasma; AUC, area under the curve; CMI, cardiometabolic index; CVD, cardiovascular disease; LAP, lipid accumulation product; NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; VAI, visceral adiposity index.

