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Threshold effect of non-high-density lipoprotein to high-density lipoprotein cholesterol ratio and hypertension in U.S. adults

NHANES 2005–2016

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Abstract

Hypertension is a prevalent chronic non-communicable disease associated with cardiovascular issues, strokes, kidney disorders, and depression. Most hypertensive patients have dyslipidemia and metabolic abnormalities. The non-high-density lipoprotein to high-density lipoprotein cholesterol ratio (NHHR) is a novel index that more accurately assesses the risk of atherosclerotic cardiovascular diseases and metabolic issues like insulin resistance. The association between NHHR and hypertension prevalence is still unclear. The study aims to examine the link between NHHR and hypertension prevalence in American adults. **N**10,410 adults from the National Health and Nutrition Examination Survey (NHANES) (2005–2016) were included in this cross-sectional analysis. Multivariable logistic regression constructed to analyze the relationship between NHHR and hypertension, with additional analyses including restricted cubic spline regression (RCS), threshold and saturation effect analyses, effect point calculations, subgroup analyses, and sensitivity analyses. Machine learning methods combined with the Boruta algorithm were employed to identify key predictors of hypertension risk. Of the 10,410 participants, 48% were male, with a hypertension prevalence of 37.03%. NHHR was higher in hypertensive patients compared to non-hypertensive individuals (2.74 vs 2.90, $P < .001$). In models that were completely confounded with factors including general demographic data, BMI, smoking status, alcohol consumption, diabetes, total cholesterol, history of coronary heart disease, LDL, and dietary cholesterol, NHHR showed a significant positive correlation with hypertension prevalence. RCS regression indicated a non-linear relationship, with a saturation effect point at 3.058. Subgroup analyses showed significant interactions by race and education level ($P < .05$). Machine learning models demonstrated AUCs > 0.8, affirming the importance of NHHR in predicting hypertension. NHHR levels are significantly elevated in hypertensive individuals compared to non-hypertensive adults in the U.S. Furthermore, a non-linear positive correlation exists between NHHR and hypertension risk, suggesting its potential as a predictive biomarker for early hypertension prevention.

Abbreviations: BMI = body mass index, CI = confidence intervals, CVD = cardiovascular disease, HDL-C = high density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, NHANES = National Health and Nutrition Examination Survey, NHHR = non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio, non-HDL-C = non-high-density lipoprotein cholesterol, OR = odds ratios, PIR = person income ratio, RCS = restricted cubic spline regression, TC = total cholesterol.

Keywords: hypertension, NHANES, NHHR, random forest, XGBoost

YS and YC contributed equally to this study.

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The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the National Centre for Health Statistics.

The authors have no conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

All NHANES data for this study are publicly available and can be found here: https://wwwn.cdc.gov/nchs/nhanes/, and every participant provided written consent.

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1. Introduction

Hypertension affects over 1 billion people worldwide and is one of the most common chronic non-communicable diseases. It is also the primary risk factors for cardiovascular diseases, strokes, and kidney disorders,[1] and it exacerbates mental health issues such as depression.[2] In the U.S., approximately 45% of adults are diagnosed with hypertension, highlighting it as a critical public health concern.[3] The updated 2017 ACC/AHA guidelines recommend universal screening, resulting in increased diagnoses and healthcare burdens.[4] Projections suggest that by 2034, global deaths from hypertension-related heart disease will rise to 1.57 million, especially in low- and middle-income areas.[5] Identifying a reliable biomarker for early prevention and subsequent management of hypertension risk is essential.

Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) has emerged as one of the valuable ratio for assessing atherosclerosis and cardiovascular disease (CVD) risks.[6] Studies indicate that hypertensive patients exhibit higher dyslipidemia and oxidative stress levels, promoting atherosclerosis.[7,8] Modifiable risk factors, including smoking, metabolic syndrome, obesity, alcohol consumption, and physical inactivity, are closely linked to dyslipidemia.[9,10] Elevated NHHR is linked to dyslipidemia, which can contribute to hypertension and subclinical atherosclerosis,[11] thereby increasing cardiovascular risk. Moreover, NHHR has shown greater predictive efficacy for insulin resistance than traditional lipid measures,[12] with insulin resistance often coexisting with hypertension,[13] and related to metabolic dysregulation and oxidative stress.[14–16] Despite these associations, evidence linking NHHR to hypertension remains limited, and no interpretable machine learning models currently emphasize NHHR's predictive value for hypertension risk.

The objective of our study endeavor was to investigate the correlation between NHHR levels and hypertension among U.S. adults utilizing data from NHANES (2005–2016) and to enhance understanding of this relationship for improved hypertension management and cardiovascular risk evaluation.

2. Materials and methods

2.1. Study population

In our study, data from the National Health and Nutrition Examination Survey (NHANES) administered by the US Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS) were used. This study is a cross-sectional observational study and is reported following STROBE guidelines to ensure proper reporting of observational studies. All procedures were approved by the Ethics Review Board (ERB) of the NCHS to ensure that the study involving participants protected the rights and welfare of participants and complied with U.S. federal regulations, and the protocol number approved for the detailed ethical review can be found at the following link: https://wwwn.cdc.gov/nchs/nhanes/, and informed consent was obtained from all participants in accordance with the Declaration of Helsinki. The NHANES data includes structured health interview survey and a physical fitness survey. In total 60,963 participants were screened from NHANES between 2005 and 2016. We included participants who met the following criteria: were 20 years of age or older at the time of the survey; NHHR calculations and diagnostic data for hypertension are complete; and Key covariate data are fully available. In addition, excluded participants based on the following criteria: those aged under 20 years (n = 26,756); missing NHHR calculations or hypertension diagnoses (n = 3251; n = 51); and missing key covariate data, including dietary cholesterol (n = 5360), history of coronary heart disease (n = 74), alcohol consumption (n = 564), low-density lipoprotein (n = 12,295), education level (n = 1884), body mass index (BMI) (n = 253), and other missing data (n = 83). Missing data were handled through listwise deletion, excluding participants with incomplete data for key variables. In addition, we conducted a sensitivity analysis to assess the robustness of the results. Ultimately, 10,410 eligible participants were included in the final analysis. Figure 1 illustrates this selection process.

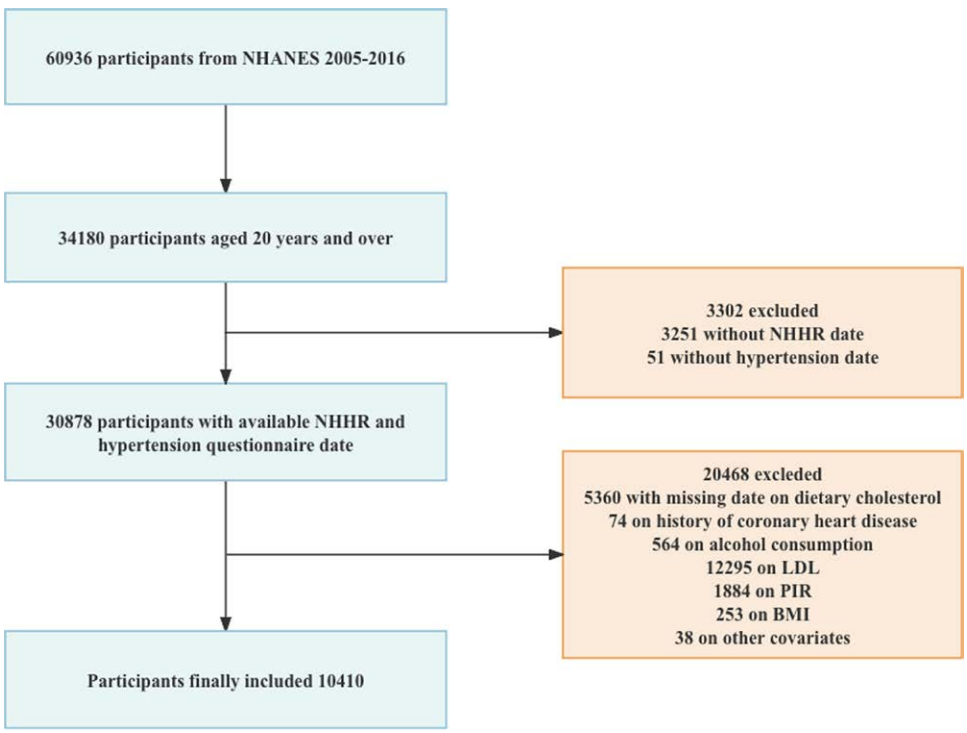

Figure 1. Flowchart of the population included in our study.

2.2. NHHR

The calculation formula for NHHR is: NHHR = Non-HDL - C/HDL-C. Non-HDL-C = TC - HDL-C. TC levels were measured using the Cholesterol Oxidase Method or the Trinder method on the Roche Modular P biochemical analyzer (Roche Diagnostics GmbH, Mannheim, Germany) and non-high-density lipoprotein cholesterol (HDL-C) levels were measured using the HDL-C-specific Trinder method or PEG-modified cholesterol oxidase method on Cobas 6000 Chemistry Analyzer (Roche Diagnostics GmbH). All experiments were performed in accordance with Roche's recommended operating practices and methods to ensure the accuracy and consistency of the analysis process.

2.3. Hypertension assessment

Hypertension was based on the NHANES official questionnaire item: "Has a doctor or other health professional ever told you that you have high blood pressure?" Participants answering "yes" were classified as hypertensive.

2.4. Covariates

Adjusted for potential confounders between NHHR and hypertension, including socio-demographics, lifestyle, and health-related factors. Sociodemographic variables were collected from standardized household interviews and included age, gender, race, education level, marital status, and poverty-to-income ratio. Lifestyle confounding variables included smoking, alcohol consumption, and dietary cholesterol intake. Smoking was categorized as never smokers and smokers, with smokers defined as those who had smoked at least 100 cigarettes. Alcohol consumption was classified as nondrinkers and drinkers, with drinkers defined as those who consumed at least 12 alcoholic beverages in the past year. Dietary cholesterol intake data were obtained from a nutrient intake questionnaire using the average of two 24-hour dietary recalls.

Health-related variables included BMI, TC, low-density lipoprotein cholesterol (LDL-C), and history of diabetes and coronary heart disease. BMI was calculated by dividing weight (kg) by height squared (m^2) (kg/m^2). Serum TC and LDL-C levels were obtained from laboratory data, all were measured using the Cholesterol Oxidase Method or the Trinder method on the Roche Modular P biochemical analyzer (Roche Diagnostics GmbH, Mannheim, Germany), with detailed methods referenced in the NHANES laboratory procedures manual. Diabetes history was based on self-reported physician diagnoses, while coronary heart disease was determined from responses to the question, "Has a doctor or other health professional ever told you that you have coronary heart disease?" A "yes" response indicated a diagnosis of coronary heart disease.

2.5. Statistical analysis

Because NHANES employs a complex, stratified sampling design, we incorporated appropriate sample weights, clustering, and stratification in all analyses to ensure the representativeness of the selected sample. The sampling weight used was WTDR2D, based on 2-day dietary intake. Continuous variables are presented as means and standard deviation (SD), while categorical variables are expressed as frequencies and percentages (n (%)). We performed a normality test using the Lilliefors test for continuous variables such as TC, LDL-C, NHHR, and Dietary Cholesterol, and none of these variables were normally distributed ($P < .05$). Therefore, we chose a non-parametric test method to better adapt to the distribution characteristics of the data. For the association between groups, The Wilcoxon rank-sum test (Mann–Whitney U test) is used for continuous variables because it does not rely on the assumption of normal distribution and is suitable for continuous or ordinal variable comparisons in complex survey designs. Rao and Scott's second-order adjusted chi-square test is used for categorical variables to more accurately reflect the effects of complex sampling designs, correct for design effects, and provide accurate p-values. Multivariable logistic regression models were used to assess the relationship between NHHR and hypertension, calculating OR and 95% CI. Participants were divided into 4 groups based on NHHR quartiles, with Q1 serving as the reference group. The NHHR quartiles were defined as follows: Q1: 0.31–1.91 (n = 2695), Q2: 1.92–2.60 (n = 2654), Q3: 2.61–3.47 (n = 2510), Q4: 3.48–26.7 (n = 2651). The Q1 group represents individuals with lower NHHR levels, characterized by lower BMI, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and fewer comorbidities. The Q2 group represents individuals with moderate NHHR levels, with intermediate BMI, TC, and LDL-C values. The Q3 group includes individuals with higher NHHR levels, with a higher BMI and a relatively higher prevalence of hypertension. The Q4 group represents individuals with the highest NHHR levels, characterized by the highest BMI and the highest prevalence of hypertension. Model 1 included no covariate adjustments; Model 2 adjusted for demographic variables such as sex, age, race, marital status, education level, and person income ratio (PIR); Model 3 further adjusted for BMI, smoking status, alcohol consumption, diabetes history, TC, coronary heart disease history, LDL-C, and dietary cholesterol intake.

Restricted cubic spline regression (RCS) regression was used to examine the linear dose-response relationship. Given that sex, race, and education are significant risk factors for hypertension and most cardiovascular diseases,[17,18] our RCS analysis was stratified by these variables. Potential nonlinear associations, including threshold or saturation effect points, were further assessed using segmented regression. Subgroup analyses were conducted to evaluate the consistency of the results. Additionally, sensitivity analyses were performed excluding individuals with hypercholesterolemia to verify the robustness of the results.

The study employed various models for feature selection and predictive analysis to enhance accuracy and interpretability. LASSO regression and the Boruta algorithm were employed to identify key features for predicting hypertension and cardiovascular disease risk, reducing overfitting and improving model reliability. For LASSO regression, the optimal regularization parameter (λ) was determined through a grid search method, minimizing misclassification error rates across a range of λ values, thereby enhancing model stability and consistency. Model performance was evaluated using the area under the curve (AUC) of receiver operating characteristic (ROC) curves. The optimal regularization parameter (λ) was determined by analyzing the misclassification error rates across different λ values to further optimize model stability and consistency. Model performance was assessed using ROC curves. To validate the models, cross-validation techniques were applied. The cross-validation results were used to estimate the model's generalizability and reduce overfitting. Based on features selected by LASSO, a Random Forest (RF) model was developed, with the number of trees (n_estimators) optimized using random search. This approach aimed to balance prediction stability and computational efficiency by averaging the results of multiple decision trees to reduce variance. Variable importance scores were generated to identify the most impactful predictors, and the model's performance was also assessed using AUC. An XGBoost (Extreme Gradient Boosting) model was constructed to enhance predictive performance, using Bayesian optimization to tune key hyperparameters, such as the learning rate (eta), maximum tree depth, and subsample ratio. SHAP (Shapley Additive Explanations) values were utilized to interpret model outputs, providing insights into how different features influenced predictions across value ranges and clarifying the decision-making process.

Table 1

Weighted baseline characteristics of included participants

Characteristic	N*	Overall N = 81,362,959†	Without hypertension N = 53,923,016†	With hypertension N = 27,439,943†	*P* value‡
Sex	10,410				.555
Male		4961 (48%)	3141 (48%)	1820 (47%)	
Female		5449 (52%)	3414 (52%)	2035 (53%)	
Age	10,410				<.001
<60		6844 (73%)	5195 (83%)	1649 (52%)	
≥60		3566 (27%)	1360 (17%)	2206 (48%)	
Race	10,410				<.001
Mexican		1545 (7.6%)	1130 (8.9%)	415 (4.9%)	
Other hispanic		937 (4.9%)	635 (5.6%)	302 (3.5%)	
Non-hispanic white		5019 (71%)	3077 (70%)	1942 (73%)	
Non-hispanic black		2033 (10%)	1069 (8.8%)	964 (12%)	
Other race		876 (6.7%)	644 (9.8%)	232 (6%)	
Education level	10,410				<.001
Less than 9th		929 (4.8%)	533 (4.1%)	396 (6.1%)	
9–11th		1453 (11%)	842 (9.9%)	611 (12%)	
High School		2374 (22%)	1397 (21%)	977 (25%)	
Some College		3057 (31%)	1950 (31%)	1107 (32%)	
College Graduate		2597 (31%)	1833 (34%)	764 (25%)	
Marital status	10,410				<.001
Married		5593 (56%)	3462 (54%)	2131 (60%)	
Widowed		815 (5.9%)	285 (3.2%)	530 (11%)	
Divorced		1111 (11%)	617 (9.7%)	494 (12%)	
Separated		304 (2.0%)	179 (1.8%)	125 (2.3%)	
Never married		1774 (18%)	1407 (22%)	367 (9.2%)	
Living with partner		813 (7.9%)	605 (9.5%)	208 (4.8%)	
Drink alcohol	10,410				<.001
No		2934 (28%)	1705 (21%)	1229 (28%)	
Yes		7476 (72%)	4850 (79%)	2626 (72%)	
BMI	10,410				<.001
<25		3050 (31%)	2352 (37%)	698 (19%)	
25–30		3459 (33%)	2236 (33%)	1223 (31%)	
≥30		3901 (36%)	1967 (30%)	1934 (49%)	
NHHR	10,410	2.79 ± (1.23)	2.74 ± (1.18)	2.90 ± (1.30)	<.001
Diabetes	10,410				<.001
No		8883 (89%)	6079 (94%)	2804 (78%)	
Yes		1297 (9.2%)	390 (4.2%)	907 (19%)	
Borderline		230 (2.0%)	86 (1.4%)	144 (3.2%)	
Smoking status	10,410				<.001
No		5702 (54%)	3795 (57%)	1907 (47%)	
Yes		4708 (46%)	2760 (43%)	1948 (53%)	
TC	10,410	194.24 ± (40.64)	194.32 ± (39.59)	194.07 ± (42.65)	.661
LDL-C	10,410	115.35 ± (35.24)	116.17 ± (34.21)	113.73 ± (37.14)	.006
Dietary cholesterol	10,410	285.66 ± (178.68)	286.72 ± (180.24)	283.59 ± (175.58)	.742
Coronary heart disease	10,410				<.001
No		9971 (96%)	6461 (99%)	3510 (92%)	
Yes		439 (4%)	94 (1.1%)	345 (8.4%)	
Income-poverty ration	10,410				.017
<1.3		3122 (30%)	1935 (21%)	1187 (22%)	
1.3–3.49		3993 (38%)	2470 (35%)	1523 (38%)	
≥3.5		3295 (32%)	2150 (44%)	1145 (40%)	

BMI = body mass index, LDL-C = low-density lipoprotein cholesterol, NHHR = non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio, TC = total cholesterol.

*N not Missing (unweighted).

†n (unweighted) (%); Mean ± (SD).

‡Chi-squared test with Rao & Scott's second-order correction; Wilcoxon rank-sum test for complex survey samples.

All data analyses were conducted using R software (4.3.2), The following R packages were used for the analyses: glmnet for LASSO regression, randomForest for Random Forest analysis, and xgboost for XGBoost modeling. A P values < .05 considered statistically significant.

3. Results

3.1. Baseline characteristics of participants

Table 1 presents the baseline characteristics based on hypertension, with the data weighted accordingly. A total of 10,410 participants, males accounted for 48% of the sample, with a hypertension prevalence of 37.03%. The average NHHR of hypertensive patients was significantly higher in non-hypertensive individuals (2.74 vs 2.90, $P < .001$). Hypertensive patients were primarily aged over 60, with a BMI ≥ 30 kg/m², mostly non-Hispanic White, and educated to at least the 9th grade. Most had low household incomes (PIR < 3.5) and histories of coronary heart disease, diabetes, and smoking, along with higher LDL-C levels. Significant differences in hypertension status were observed for age, race, education, marital status, alcohol consumption, BMI, NHHR, diabetes, smoking,

Table 2

Weighted baseline characteristics of included participants are stratified by NHHR quartiles

Characteristic	N*	Overall N = 81,362,959†	Q1 N = 20,386,615†	Q2 N = 20,318,569†	Q3 N = 20,332,392†	Q4 N = 20,325,383†	*P* value‡
Sex	10,410						<.001
Male		4961 (48%)	913 (32%)	1105 (42%)	1304 (52%)	1639 (65%)	
Female		5449 (52%)	1782 (68%)	1549 (58%)	1206 (48%)	912 (35%)	
Age	10,410						<.001
<60		6844 (73%)	1708 (69%)	1656 (69%)	1656 (75%)	1824 (79%)	
≥60		3566 (27%)	987 (31%)	998 (31%)	854 (25%)	727 (21%)	
Race	10,410						<.001
Mexican		1545 (7.6%)	294 (5.8%)	380 (7.1%)	416 (7.9%)	455 (9.5%)	
Other hispanic		937 (4.9%)	185 (4.2%)	214 (3.9%)	264 (5.3%)	274 (6.1%)	
Non-hispanic white		5019 (71%)	1271 (69%)	1267 (71%)	1234 (73%)	1247 (70%)	
Non-hispanic black		2033 (10%)	678 (14%)	557 (10%)	428 (8.3%)	370 (7.7%)	
Other race		876 (6.7%)	267 (2.56%)	236 (2.27%)	168 (1.61%)	205 (1.97%)	
Education level	10,410						<.001
Less Than 9th		929 (4.8%)	171 (3.8%)	249 (5.0%)	235 (4.3%)	274 (6.0%)	
9–11th		1453 (11%)	337 (9.4%)	338 (9.2%)	357 (11%)	421 (13%)	
High School		2374 (22%)	523 (19%)	577 (21%)	635 (25%)	639 (26%)	
Some College		3057 (31%)	816 (31%)	780 (31%)	742 (33%)	719 (29%)	
College Graduate		2597 (31%)	848 (37%)	710 (34%)	541 (26%)	498 (26%)	
Marital status	10,410						<.001
Married		5593 (56%)	1295 (52%)	1414 (56%)	1417 (57%)	1467 (58%)	
Widowed		815 (5.9%)	262 (7.3%)	218 (6.3%)	182 (5.2%)	153 (4.6%)	
Divorced		1111 (11%)	256 (9.2%)	295 (11%)	274 (11%)	286 (12%)	
Separated		304 (2.0%)	83 (1.6%)	69 (2.1%)	77 (2.3%)	75 (1.8%)	
Never married		1774 (18%)	595 (22%)	461 (17%)	372 (17%)	346 (15%)	
Living with partner		813 (7.9%)	204 (8.0%)	197 (7.0%)	188 (7.8%)	224 (8.9%)	
Drink alcohol	10,410						.345
No		2934 (28%)	750 (22%)	774 (23%)	750 (25%)	660 (23%)	
Yes		7476 (72%)	1945 (78%)	1880 (77%)	1760 (75%)	1891 (77%)	
BMI	10,410						<.001
<25		3050 (31%)	1306 (54%)	829 (34%)	549 (23%)	366 (13%)	
25–30		3459 (33%)	760 (26%)	895 (32%)	889 (35%)	915 (38%)	
≥30		3901 (36%)	629 (20%)	930 (35%)	1072 (42%)	1270 (49%)	
Hypertension	10,410						<.001
Without hypertension		6555 (66%)	1768 (71%)	1667 (66%)	1552 (65%)	1568 (63%)	
With hypertension		3855 (34%)	927 (29%)	987 (34%)	958 (35%)	983 (37%)	
Diabetes	10,410						.254
No		8883 (89%)	2328 (90%)	2270 (88%)	2127 (90%)	2158 (87%)	
Yes		1297 (9.2%)	319 (8.3%)	331 (9.9%)	322 (8.3%)	325 (10%)	
Borderline		230 (2.0%)	48 (1.6%)	53 (1.8%)	61 (2.2%)	68 (2.5%)	
Smoking	10,410						<.001
No		5702 (54%)	1601 (58%)	1486 (55%)	1385 (54%)	1230 (48%)	
Yes		4708 (46%)	1094 (42%)	1168 (45%)	1125 (46%)	1321 (52%)	
TC	10,410	194.24 ± (40.64)	173.02 ± (34.04)	185.63 ± (35.81)	198.59 ± (36.32)	219.77 ± (40.67)	<.001
LDL-C	10,410	115.35 ± (35.24)	87.49 ± (22.99)	108.45 ± (26.09)	123.21 ± (29.16)	142.32 ± (35.99)	<.001
NHHR	10,410	2.79 ± (1.23)	1.49 ± (0.31)	2.25 ± (0.20)	3.00 ± (0.25)	4.44 ± (1.03)	<.001
Dietary cholesterol	10,410	285.66 ± (178.68)	266.11 ± (164.51)	278.14 ± (164.56)	290.07 ± (186.85)	308.38 ± (194.23)	<.001
Coronary heart disease	10,410						.090
No		9971 (96%)	2553 (96%)	2546 (96%)	2412 (97%)	2460 (97%)	
Yes		439 (4%)	142 (4.4%)	108 (3.9%)	98 (3.3%)	91 (2.7%)	
Income-poverty ration	10,410						<.001
<1.3		3122 (30%)	716 (20%)	768 (20%)	748 (20%)	890 (26%)	
1.3–3.5		3993 (38%)	1017 (35%)	1026 (35%)	1016 (40%)	934 (34%)	
≥3.5		3295 (32%)	962 (45%)	860 (45%)	746 (41%)	727 (40%)	

BMI = body mass index, LDL-C = low-density lipoprotein cholesterol, NHHR = non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio, TC = total cholesterol.

*N not Missing (unweighted).

†n (unweighted) (%); Mean ± (SD).

‡Chi-squared test with Rao & Scott's second-order correction; Wilcoxon rank-sum test for complex survey samples.

LDL-C levels, coronary heart disease history, and poverty-to-income ratio ($P < .05$).

Table 2 presents the weighted baseline characteristics of participants by NHHR quartiles. Patients in the highest NHHR quartile (Q4) were predominantly male, mostly under 60 years old, with lower educational attainment (≤11th grade) and household incomes, and higher BMI. Significant differences were found among quartiles for smoking, hypertension prevalence, TC, LDL-C, and dietary cholesterol intake ($P < .001$). Compared to Q1, Q4 participants had a higher smoking rate and significantly increased TC, LDL-C, and dietary cholesterol intake. Additionally, hypertension prevalence rose with increasing NHHR levels.

3.2. Multivariate regression analysis

Table 3 shows the multivariable logistic regression between NHHR and hypertension. The continuous model revealed a

Table 3

Association between NHHR and hypertension among US adults in NHANES 2005–2016

	Continuous models		Categorical model				
Outcomes	**OR**	***P* value**	**Q1**	**Q2**	**Q3**	**Q4**	***P* trend**
Model 1	1.11 (1.06–1.63)	<.001	1 (Ref)	1.49 (0.78–2.87)	0.97 (0.57–1.66)	1.10 (0.99–1.21)	<.001
Model 2	1.17 (1.11–1.24)	<.001	1 (Ref)	1.75 (0.75–4.07)	1.03 (0.55–1.91)	1.56 (1.03–1.30)	<.001
Model 3	1.23 (1.12–1.35)	<.001	1 (Ref)	2.08 (0.84–5.12)	1.11 (0.59–2.08)	1.16 (1.01–1.34)	<.001

Model 1 did not adjust for potential confounders.

Model 2 included adjustments for demographic variables such as sex, age, ethnicity, marital status, educational level, and PIR.

Model 3, based on Model 2, further adjusted for factors such as BMI, smoking status, alcohol consumption, diabetes, total cholesterol, history of coronary heart disease, low density lipoprotein, and dietary cholesterol.

NHHR = non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio, OR = odds ratios.

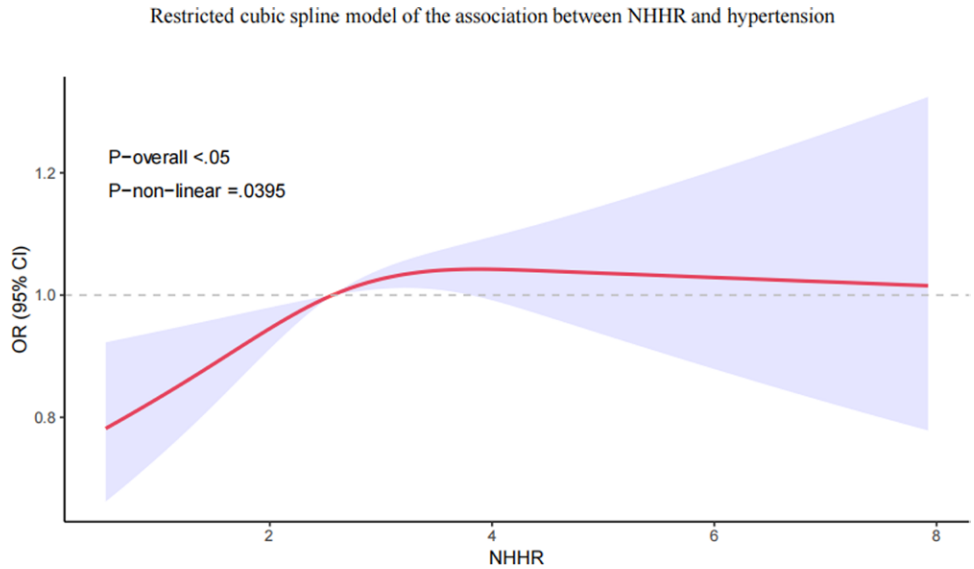

Figure 2. Restricted cubic spline model of the association between NHHR and hypertension. The relationship between NHHR (non-HDL/HDL cholesterol ratio) and the prevalence of hypertension is shown. The smoothed curve represents the adjusted odds ratio (OR) as NHHR increases, and the shaded areas represent the corresponding 95% confidence interval (CI). There was a saturation effect, with the risk of hypertension increasing slowly after the NHHR reached the saturation point of 3.058. NHHR = non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio.

significant positive correlation between NHHR and hypertension prevalence after full covariate adjustment (OR = 1.23, 95% CI: 1.12–1.35, $P < .001$). In the categorical model, Model 3 maintained this significant association (OR = 1.16, 95% CI: 1.01–1.34, $P < .05$), indicating that each 1-unit increase in NHHR increases hypertension risk by 16%. Trend analysis confirmed a significant relationship between rising NHHR and hypertension risk, with ORs increasing from Q1 to Q4 and p trends < 0.001, indicating statistical significance.

3.3. Non-linear analysis

RCS analysis showed a non-linear association between NHHR and risk of hypertension (P non-linear = 0.3291), as shown in Figure 2. The adjusted smooth curve suggests a saturation effect in the relationship between NHHR and hypertension prevalence. All P value was < .05, indicating statistical significance and supporting the impact of NHHR level changes on hypertension risk.

Age-stratified RCS revealed differing non-linear associations between NHHR and hypertension in males and females, with females showing a higher risk at elevated NHHR levels (Fig. 3). Education-stratified RCS results (Fig. 4) indicated that as education level increased, the influence of NHHR on hypertension risk diminished. In the low education group (1 = Less Than 9th grade), the hypertension risk plateaued at higher NHHR levels, suggesting a saturation effect. Race-stratified RCS (Fig. 5) showed that non-Hispanic Black individuals had a significantly increased hypertension risk at higher NHHR levels, while risks for other races remained relatively stable.

Further analysis using two-segment regression determined the saturation effect point for NHHR at 3.058 (Table 4). Beyond an NHHR of 3.058, the trend flattened but remained statistically significant.

3.4. Subgroup analysis

Subgroup analyses assessed the robustness of the relationship between NHHR and hypertension in relation to demographic characteristics and comorbidities, as shown in Figure 6. No significant interaction effects were found across age, sex, marital status, PIR, BMI, smoking, alcohol consumption, diabetes, and coronary heart disease strata (P for interaction > .05), indicating consistent results. However, race and education level significantly altered the association between NHHR and hypertension, demonstrating a notable interaction (P for interaction < .05).

3.5. Sensitivity analyses

Sensitivity analysis was conducted by excluding participants with hypercholesterolemia. In the fully adjusted categorical model, the association between NHHR of the Q4 group and

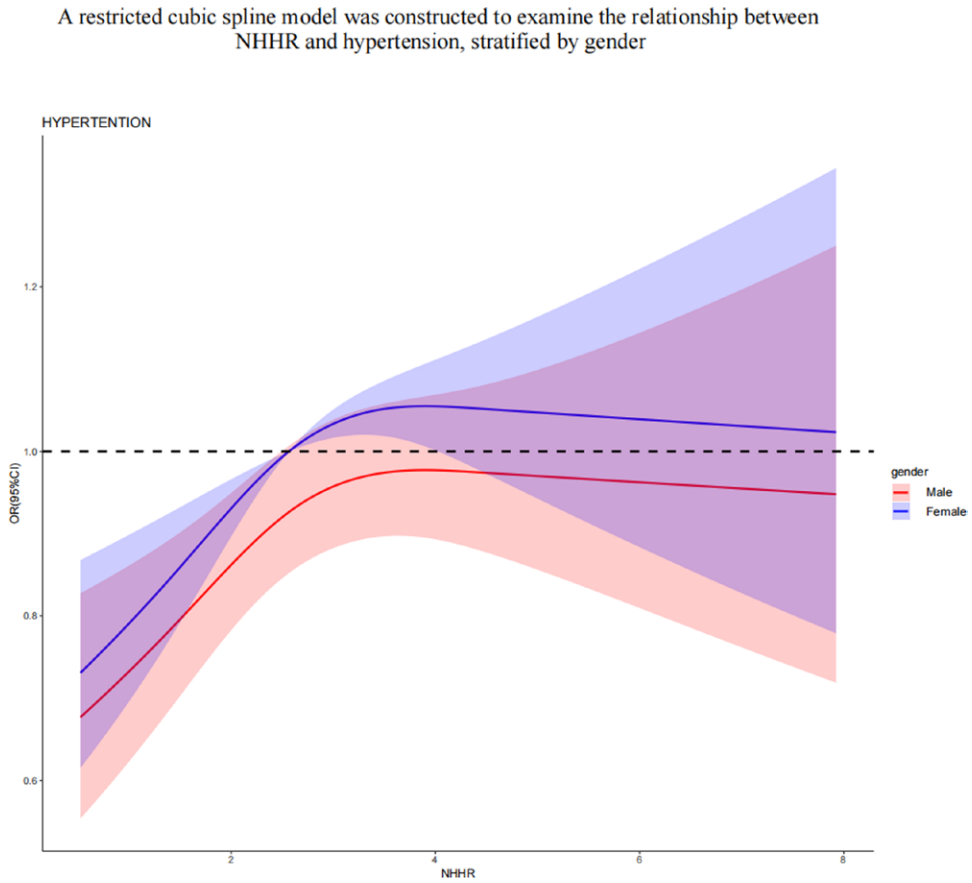

Figure 3. A restricted cubic spline model was constructed to examine the relationship between NHHR and hypertension, stratified by gender (1 = Male, 2 = Female). The red group represents the male group and the blue group represents the female group. With the increase of NHHR, the risk of hypertension showed a significant difference between men and women, and the risk of hypertension increased significantly in the female group when NHHR was high. The smoothed curve represents the adjusted odds ratio (OR) as NHHR increases, and the shaded areas represent the corresponding 95% confidence interval (CI). NHHR = non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio.

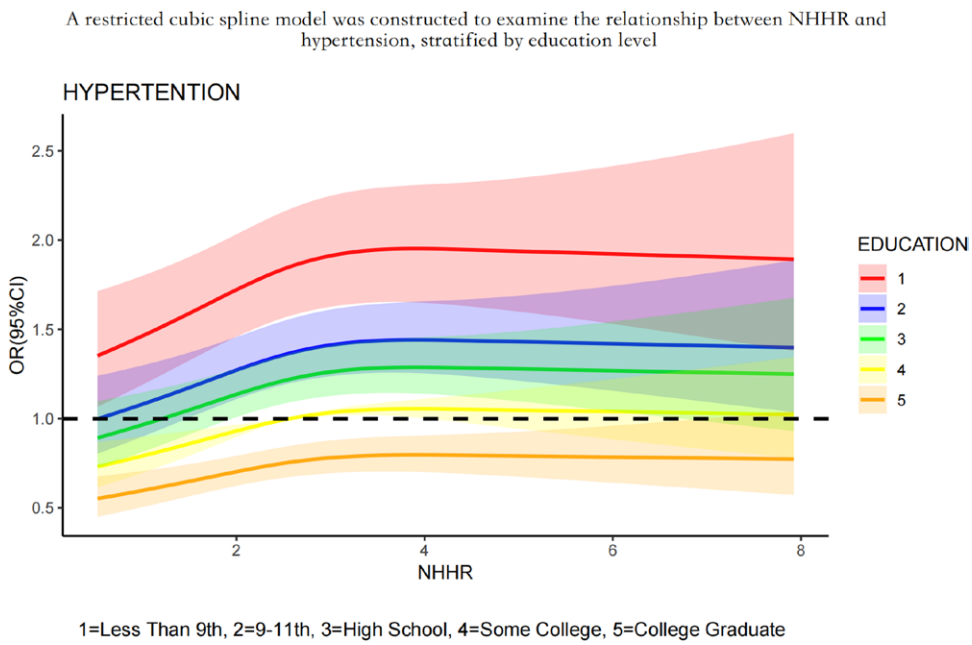

Figure 4. A restricted cubic spline model was constructed to examine the relationship between NHHR and hypertension, stratified by education level (1 = Less Than 9th, 2 = 9–11th, 3 = High School, 4 = Some College, 5 = College Graduate). The red group represents Less Than 9th, the blue group represents 9–11th, and the green group represents High School The yellow group represents Some College, and the orange group represents College Graduate. With the increase in NHHR, the risk of hypertension in all education levels is gradually increasing. The increased risk of hypertension in groups with low educational attainment (e.g., less than grade 9) is more pronounced when NHHR increases, with a saturation effect. The smoothed curve represents the adjusted odds ratio (OR) as NHHR increases, and the shaded areas represent the corresponding 95% confidence interval (CI). NHHR = non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio.

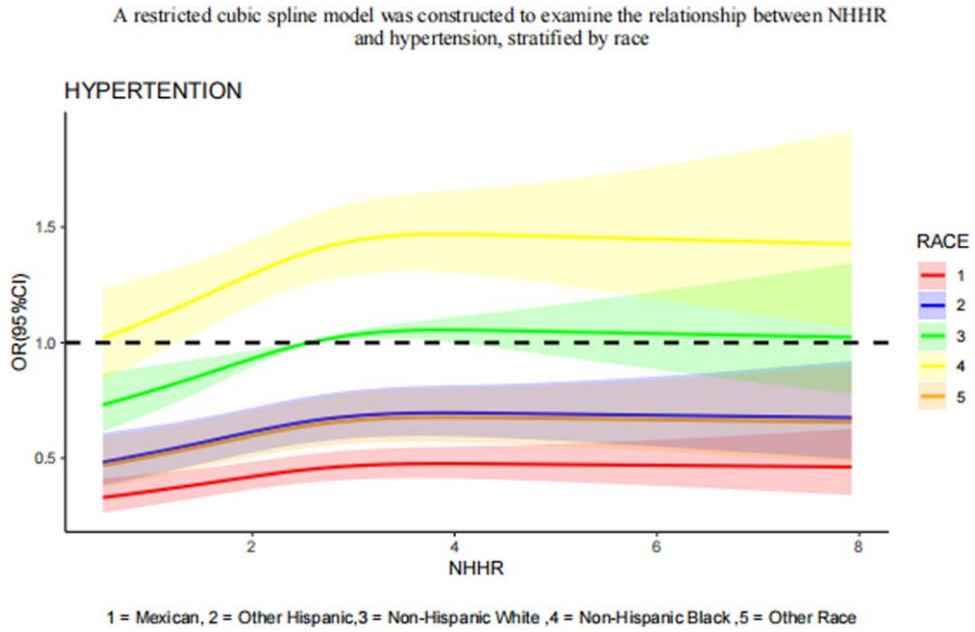

Figure 5. A restricted cubic spline model was constructed to examine the relationship between NHHR and hypertension, stratified by race (1 = Mexican, 2 = Other Hispanic, 3 = Non-Hispanic White, 4 = Non-Hispanic Black, 5 = Other Race). The red group represents Mexicans, the blue group represents other Hispanics, the green group represents non-Hispanic whites, the yellow group represents non-Hispanic blacks, and the orange group represents other races. The risk of hypertension in non-Hispanic blacks increases significantly when NHHR increases. The smoothed curve represents the adjusted odds ratio (OR) as NHHR increases, and the shaded areas represent the corresponding 95% confidence interval (CI). NHHR = non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio.

Table 4

Threshold effect analysis of NHHR on hypertension

	Adjusted OR (95% CI)	*P* value
Fitting by standard linear model NHHR	1.196 (1.133, 1.263)	<.0001
Fitting by two-piece wise model		
Inflection point	3.058	
NHHR < 3.058	1.380 (1.239, 1.537)	<.0001
NHHR > 3.058	1.115 (1.040, 1.196)	.0022
Likelihood ratio test		.0030

CI = confidence intervals, NHHR = non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio, OR = odds ratios.

hypertension remained significant ($P > .05$). A significant trend across different groups was also observed (P for trend < .05), in Table 5.

3.6. Model feature selection, construction and interpretation

The LASSO regression results, shown in Figure 7, revealed 15 significant features impacting prediction, including age, sex, race, education, marital status, PIR, BMI, smoking, alcohol consumption, coronary heart disease history, diabetes history, total cholesterol, LDL-C, dietary cholesterol, and NHHR. At lambda.1se, 10 key features were retained, simplifying the model and enhancing its generalizability. Importance ranking indicated that age, BMI, smoking, sex, and NHHR were dominant predictors. The ROC curve yielded an AUC of 0.814, reflecting good classification performance.

Building on the LASSO-selected features, the random forest model results are presented in Figure 8. Key influencing features included age, diabetes, LDL-C, BMI, marital status, and total cholesterol. As the number of decision trees increased, the out-of-bag (OOB) error rate decreased and stabilized at a low level, indicating model robustness. The AUC was 0.807, demonstrating good classification performance.

The XGBoost model results, shown in Figure 9, identified age, BMI, diabetes, race, and LDL-C as major predictors of hypertension risk, with an AUC of 0.817, indicating strong discrimination capability. SHAP analysis highlighted the specific impacts of each feature, with age being the most influential (average SHAP value of 0.821), indicating that older individuals have a higher risk of hypertension, alongside high BMI and diabetes.

The Venn diagram in Figure 10 illustrates the common important features selected by the LASSO, random forest (RF), and XGBoost models. All 3 models identified 15 shared key features, indicating complete agreement among the models and highlighting these variables as the most critical for the prediction task.

4. Discussion

The large cross-sectional study of U.S. adults, we identified significant key variables for hypertension risk prediction using 3 machine learning models. Our findings show a significant positive correlation between NHHR and the occurrence of hypertension. Regardless of the adjustment model used, increased NHHR correlates with higher hypertension prevalence, with similar results seen in sensitivity analyses. Notably, a non-linear saturation effect was observed, with a saturation point at 3.058. The models built with the 3 machine learning algorithms all yielded AUC values exceeding 0.8, underscoring NHHR's relative importance in lipid metrics.

The NHHR may serve as a potential early predictor of hypertension, highlighting the clinical significance of maintaining optimal NHHR levels for reducing hypertension risk.

NHHR as a novel lipid ratio for assessing atherosclerosis has been recognized a well predictor of cardiovascular disease risk, offering greater predictive capability than individual lipid parameters.[19] Given its advantages in evaluating lipid metabolism abnormalities, NHHR could be a valuable prospective biomarker. The inclusion of NHHR in these existing clinical risk models may improve the accuracy of risk assessment of CVD

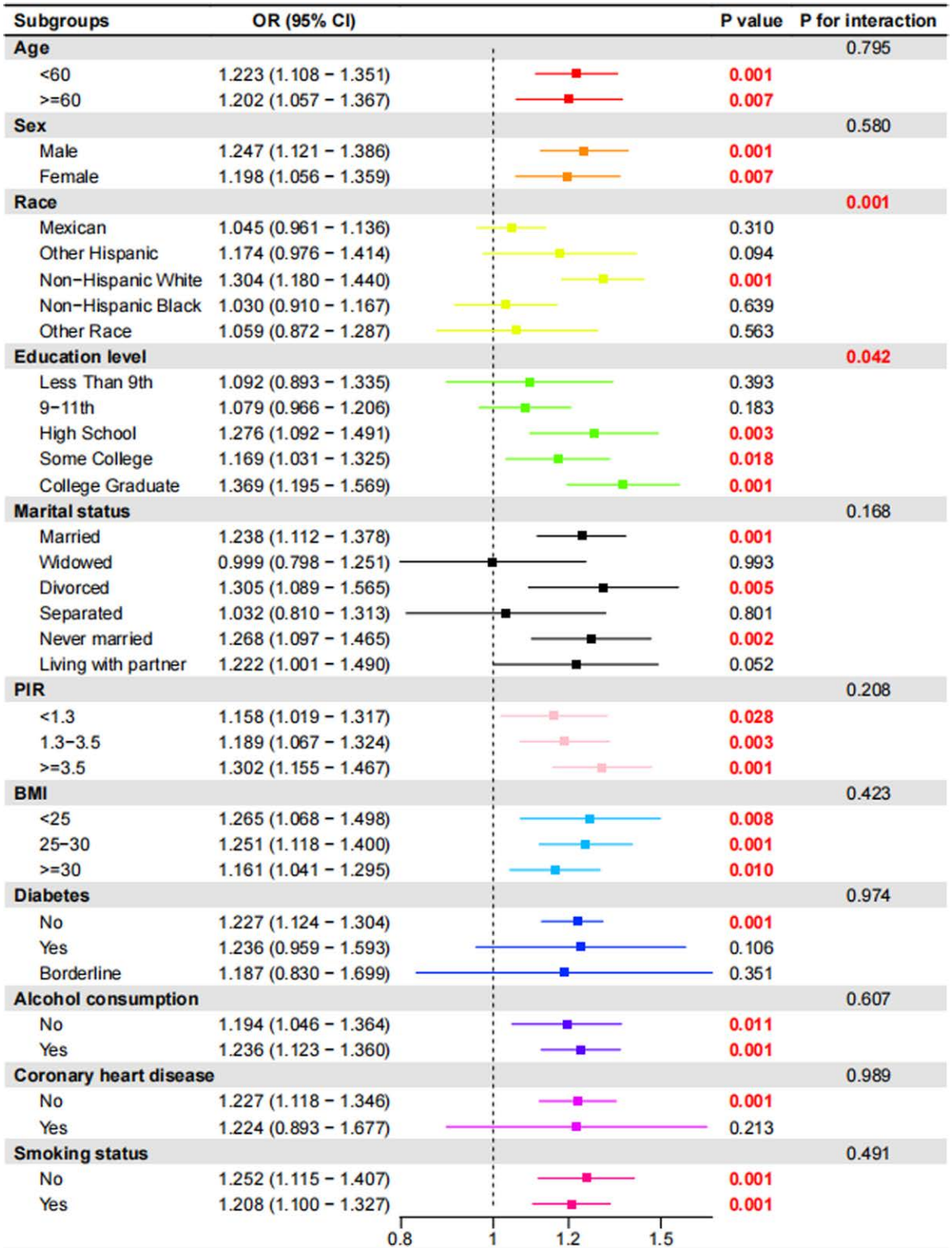

Figure 6. Subgroup analysis of association between NHHR and hypertension. NHHR = non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio.

and hypertension, providing additional prognostic value. In addition, NHHR serves as a simple and cost-effective indicator, and the inclusion of NHHR in clinical practice guidelines helps clinicians more effectively identify those high-risk individuals who may benefit from early intervention, lifestyle changes, or drug therapy, playing a key role in preventive medicine to achieve more precise and personalized treatment.

Previous studies have established a connection between hypertension and various individual or traditional lipid metrics. A Taiwan's large cohort study (2022) detected that TC/HDL-C and low HDL-C levels were significantly associated with new-onset hypertension, suggesting lipid abnormalities could aid in early hypertension risk identification.[20] In a Chinese community study, higher triglycerides and lower HDL-C were linked

to the increasing about risk of new-onset hypertension, indicating a relationship between lipid abnormalities and hypertension onset.[21] Emerging evidence highlights that imbalances between LDL-C and HDL-C are also strongly associated with the development of hypertension, especially in metabolically abnormal individuals.[22,23] The coexistence of hypertension and lipid abnormalities may exacerbate adverse effects on the cardiovascular system beyond those from single factors.[22,24] Prior clinical studies have explored the association between non-HDL-C and CVD incidence and mortality. For instance, Fukushima[25] indicated that non-HDL-C is an valid predictor of CVD mortality, especially in patients with coronary heart disease, and it increase the long-term risk of cardiovascular events. A reviews and meta-analyses showed that non-HDL-C is a superior predictor of cardiovascular events and is significantly associated with the incidence of cardiovascular disease, in patients with type 2 diabetes.[26] A multinational cardiovascular risk study further demonstrated that non-HDL-C is closely linked to long-term CVD risk across diverse populations, and that reducing non-HDL-C may significantly decrease the incidence of CVD.[27]

The mechanisms underlying the association between NHHR and hypertension have not been fully elucidated. However, studies have demonstrated that several key pathways involve multiple factors, including endothelial damage, oxidative stress, and insulin resistance. Oxidized LDL (ox-LDL) accumulates in the endothelium and intima, leading to endothelial dysfunction by generating reactive oxygen species (ROS), promoting endothelial nitric oxide synthase (eNOS) uncoupling, and reducing nitric oxide (NO) bioavailability.[28] Furthermore, ox-LDL increases the expression of adhesion molecules in endothelial cells, promoting immune cell adhesion and migration, which exacerbates vascular damage and increases hypertension risk.[29] Lipid abnormalities, such as hypercholesterolemia and elevated LDL, enhance the effects of angiotensin II (Ang II) by upregulating the expression of type 1 angiotensin II receptors (AT1R).[30] The complex formed by ox-LDL and AT1R activates downstream G protein signaling pathways, stimulating the activity of NADPH oxidase and increasing ROS production. These ROS amplify Ang II signaling,[31] and damage endothelial cells through oxidative stress, further worsening vascular dysfunction. Additionally, activation of this complex via the MAPK/ERK pathway promotes smooth muscle cell proliferation and vascular remodeling, contributing to atherosclerosis and enhancing vascular contraction, thereby facilitating hypertension.[32] Moreover, unhealthy lifestyles and high-fat diets, resulting in excessive production of adipokines such as leptin, which promote vascular remodeling via the p38 MAPK pathway, increasing hypertension risk.[33] Insulin resistance also heightens hypertension risk by disrupting lipid metabolism and vascular function. Insulin sensitizers, such as PPAR-γ agonists, can reduce oxidative and endoplasmic reticulum stress, restore NO levels, lower blood pressure, and improve cardiovascular complications.[34,35] These agents also enhance angiogenesis and prevent endothelial cell apoptosis, indirectly improving vascular function and promoting blood pressure reduction.[36] In states of hypercholesterolemia and insulin resistance, circulating levels of endothelin-1 (ET-1) and Ang II increase, enhancing AT1R activity, which collectively upregulates vascular tone and promotes blood pressure elevation. Additionally, pressure receptor sensitivity is reduced, thus predisposing to sympathetic activation and hypertension development.[37] Our findings indicating

Table 5

Sensitivity analyses

	OR	*P* for value	*P* for trend
Excluding participants with hypercholesterolemia			.002
Q1	1 (Ref)		
Q2	0.43 (0.13–1.39)	.163	
Q3	0.80 (0.32–2.03)	.645	
Q4	1.27 (1.02–1.58)	.033	

The sensitivity analysis used the model3 fully adjusted model.
OR = odds ratios.

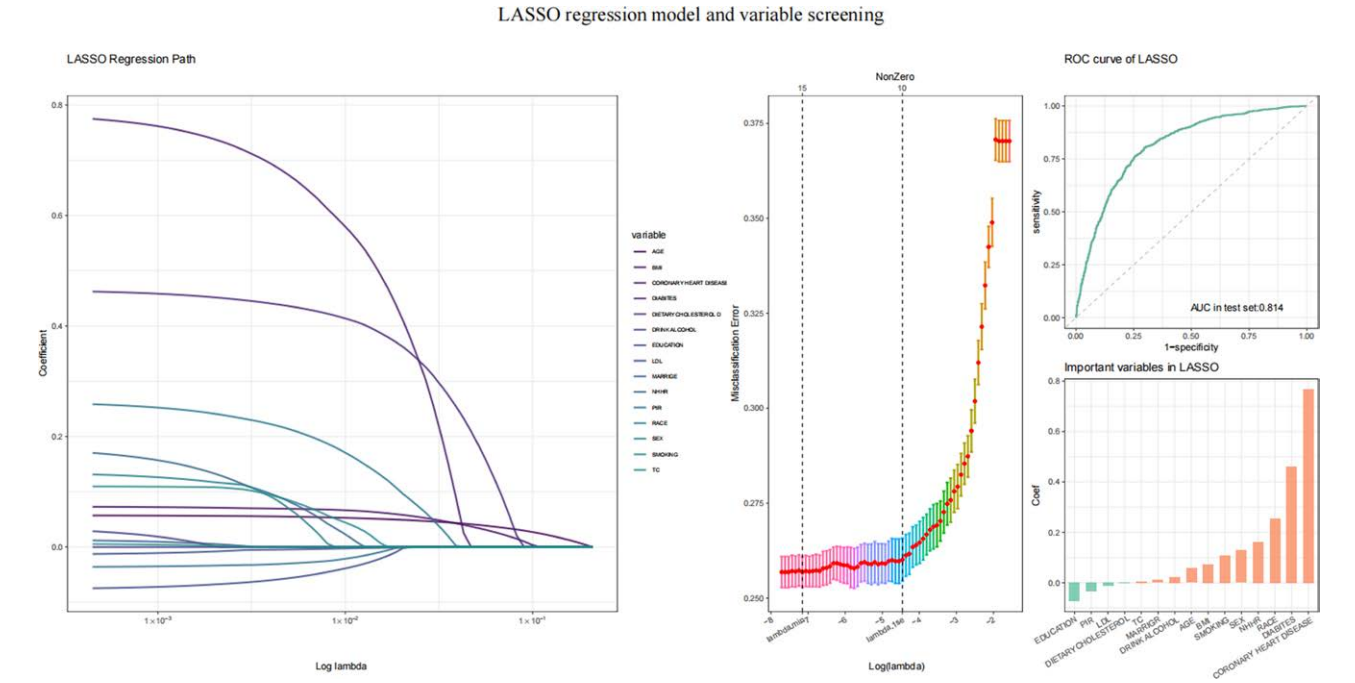

Figure 7. LASSO regression model and variable screening. Left image: Regression coefficient profile. Each curve represents the trajectory for each eigenco-efficient. Middle image: Cross-validation error of the LASSO model. The colored areas represent the standard error, and each red dot represents the mean square error (MSE) for each λvalue. Top right image: ROC curve of the LASSO model. Bottom right image: Bar chart showing important variables in the LASSO regression model. The bar length indicates the magnitude of the influence of the variable on the prediction of hypertension.

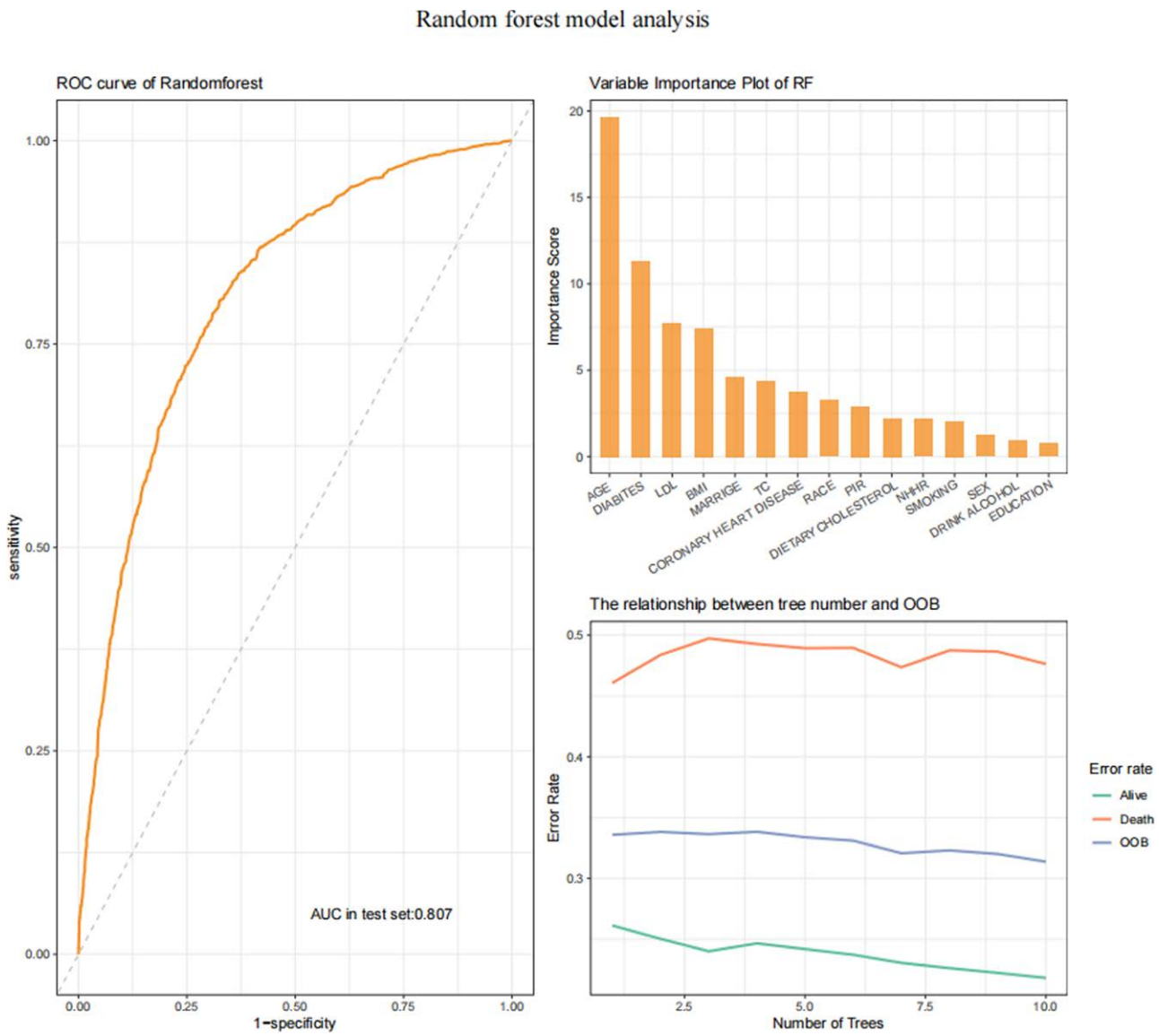

Figure 8. Random forest model analysis. Left image: ROC curve of the RF model. Top right image: Importance plot of each variable in a random forest model. The bar chart represents the contribution of the variable to the model. Bottom right image: The relationship between the number of trees and training error, test error, and OOB error. The blue, green, and red figures represent the training error, test error, and OOB error, respectively.

a nonlinear saturation effect between NHHR and hypertension prevalence (*P* non-linear = 0.3291). Through threshold saturation relationship analysis based on RCS, we determined the saturation effect point to be 3.058. When NHHR exceeds 3.058, the increase in hypertension risk becomes less pronounced. This novel finding from nonlinear analysis may more accurately reflect the true relationship about NHHR and hypertension. Notably, a large-scale health examination study in Japan found a U-shaped relationship between HDL-C and hypertension.[38] Similar results also were reported by Trimarco et al[39] This may be exhibit both anti-inflammatory and pro-inflammatory effects of HDL-C.[40,41] Furthermore, while increasing HDL-C levels theoretically reduces cardiovascular risk, actual clinical trial outcomes indicate that merely raising HDL-C does not significantly decrease cardiovascular events.[42] The nonlinear correlation with NHHR and hypertension warrants further investigation. Age-stratified RCS analysis demonstrates that the dose-response relationship differently in men and women. We found that the hypertension risk associated with high NHHR is significantly higher in females. The differences may be partially attributed to the following factors. Polymorphisms in the renin-angiotensin-aldosterone system genes contribute to sex-specific differences in blood pressure regulation. Notably, genetic variations in female hypertensive patients are significantly associated with left ventricular hypertrophy and hypertension.[8,43] In premenopausal women, the C4599A polymorphism of the angiotensin II type 2 receptor (AT2-R) gene is significantly linked with hypertension.[44] Additionally, BMI has a greater influence on blood pressure in women. Research by Park et al demonstrates that although BMI does not significantly increase in postmenopausal women, there is a notable rise in blood pressure, indicating that changes in fat distribution have a more substantial effect on blood pressure in women.[45] Our subgroup analysis further reveals that race and education level modify the relationship between NHHR and hypertension. In an observational study conducted across 9 European countries, White et al found that individuals with lower education levels exhibited poorer blood pressure control, aligning with our findings. The underlying mechanisms of this disparity may involve multiple aspects such as health literacy, lifestyle choices, and socioeconomic status. Low education levels are often associated with poor health literacy, unhealthy dietary habits, and

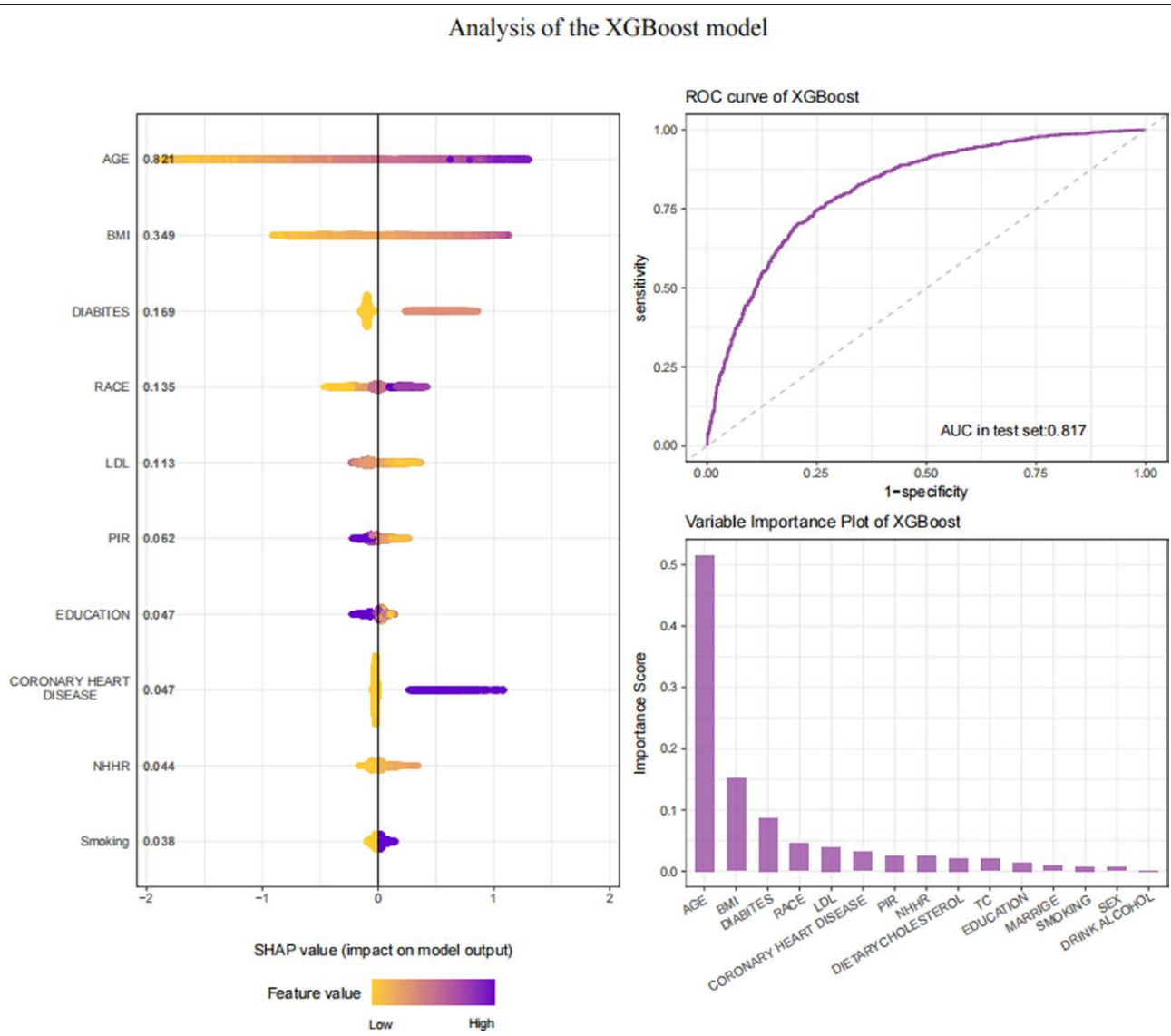

Figure 9. Analysis of the XGBoost model. Left image: Shapley Additive Explanations plot. Each dot represents the SHAP value of a eigenvalue, and the color indicates the magnitude of that eigenvalue (purple for low values and orange for high values). Top right image: ROC curve of the XGBoost model. Bottom right image: Importance diagram of each variable in the XGBoost model. The bar chart represents the contribution of each feature to the prediction outcome.

suboptimal medication adherence.[46] Individuals with lower education frequently lack knowledge and economic resources regarding healthy eating, leading them to choose unhealthy high-salt, high-fat, and high-sugar foods, thereby increasing the risk of chronic diseases such as hypertension. Interventions addressing these factors may help improve blood pressure control in this population.[47] In addition, people with low levels of education may not receive timely treatment or management of hypertension due to insufficient attention to health issues and poor access to health resources and medication adherence. Disparities in hypertension prevalence among different racial groups are partly attributable to genetic diversity and specificity, with significant differences in allele frequencies.[48] Genetic factors may influence susceptibility to hypertension by affecting blood pressure regulatory mechanisms, particularly the notably higher prevalence of hypertension among Black populations.[49] Non-Hispanic Black individuals with high cholesterol and hypertension face a significantly elevated risk of CVD compared to other racial groups.[50] Furthermore, despite lower LDL-C levels, the risk of CVD markedly increases in the presence of low HDL-C levels,[51] consistent with our findings. The high prevalence of hypertension in non-Hispanic Blacks is linked to specific gene variations that play critical roles in blood pressure regulation, supported by genome-wide association studies (GWAS) identifying significant links between certain gene loci (e.g., FGF5, ULK4, and HOXA-EVX1) and blood pressure variations in this population.[52] Variants in these genes may play an important role in the regulation of blood pressure in this population, further explaining the higher prevalence of hypertension in the black population. However, in addition to genetic factors, socioeconomic factors may also exacerbate hypertension risk in this group through gene-environment interactions.[53] Psychosocial factors, such as social support and psychological stress, may also play an impact on the onset and control of hypertension. Therefore, these differences are not only determined by genetic factors, but also environmental factors such as socioeconomic factors, lifestyle, health behaviors, etc., play an important role in it.

This study features a large and representative sample size, which enhances the credibility of the results. We adjusted for confounding variables among the important features; for example, research indicates that increasing cholesterol intake is significantly associated with a higher risk of hypertension.[54] Thus, we included cholesterol intake in fully adjusted

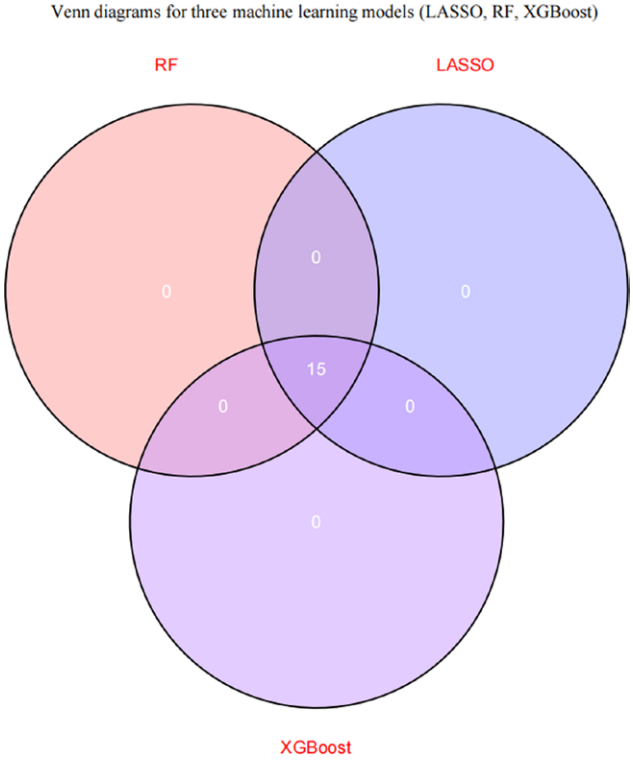

Figure 10. Venn diagrams for 3 machine learning models (LASSO, RF, XGBoost). Each circle represents the set of features selected by one model, and the overlap represents the features selected by multiple models. The "15" in the figure represents the number of features selected by the 3 models.

model to ensure the reliability of the findings. Subgroup analyses and RCS evaluations were conducted to examine the robustness of the relationship between NHHR and hypertension across different populations, revealing a nonlinear saturation relationship and calculating the potential saturation effect point.

Given that machine learning models have demonstrated superior predictive performance compared to traditional regression models in predicting hypertension risk.[55] In our study, 3 machine learning models were employed to identify several key variables that significantly influence hypertension risk, collectively identifying 15 important features. All models demonstrated commendable classification performance, with area under the curve (AUC) values exceeding 0.8. To our knowledge, this is the first application of interpretable machine learning in identifying hypertension risk. In addition to identifying shared predictive factors, machine learning models complement traditional regression methods by capturing non-linear relationships and complex interactions between variables, which traditional methods like logistic regression may not fully account for. While logistic regression excels in identifying linear associations, machine learning algorithms, such as LASSO, Random Forest, and XGBoost, are capable of detecting non-linear patterns and high-dimensional feature interactions, which improve the model's ability to make more accurate predictions. These models also help to mitigate issues related to multicollinearity and overfitting, which are common challenges in traditional regression approaches. Among these models, the XGBoost algorithm exhibited the strongest ability to distinguish hypertension risk, with an AUC of 0.817. SHAP value analysis indicated that age had the most significant impact on predictions, with an average SHAP value of 0.821, suggesting that older individuals face a higher risk of hypertension. This may be attributed to factors such as vascular stiffening, neurohormonal dysregulation, and declining renal function that are prevalent in older populations.[56] Our findings contribute to the evolving research landscape in this field, demonstrating the potential of interpretable machine learning applications in identifying hypertension risk and fostering a broader understanding of machine learning capabilities.

This study offers several significant advantages. First, we selected a large number of representative and standardized samples from the NHANES database, all of which underwent strict quality control and government supervision, and weighted the statistical analysis according to the NHANES's complex sampling design, which enhanced its national representativeness and generalizability to the U.S. population, and the adjustment of multiple confounding covariates increased the reliability of the results. Second, the study found a threshold effect between NHHR and the risk of hypertension. Finally, we used a variety of machine learning methods, such as LASSO regression, Boruta algorithm, random forest, and XGBoost model, for feature selection and predictive analysis. However, our study also has several limitations. Firstly, as cross-sectional study, it cannot establish a causal relationship between NHHR and hypertension. Therefore, future prospective longitudinal studies are needed to further validate the association and potential causal mechanisms between NHHR and hypertension. Additionally, all data were sourced from the NHANES database, which is limited to the U.S. population. Dietary habits and structures in various countries and regions have significant differences, this may affect the validity of the findings and restrict their generalizability to populations in other areas. When applying these results to different countries or cultural contexts, it is imperative to exercise caution. because differences could potentially impact the study conclusions. Although we included and adjusted for important confounding variables to mitigate potential biases, we cannot exclude the influence of all possible confounders, such as genetic factors and lifestyle influences within cultural contexts. These unadjusted confounders may partially affect the interpretation of the study results. Future research should consider further exploring the independent effects of these factors. Furthermore, certain medications, such as statins, may influence NHHR measurements, including HDL-C and non-HDL-C levels. However, this potential confounder was not explicitly addressed in the current study, and future research should consider accounting for the effects of medication use on NHHR when analyzing its association with hypertension. Moreover, all machine learning models may be prone to "overfitting," necessitating the incorporation of more training data to help the models better learn the overall characteristics of the data.

5. Conclusions

The results indicate a positive correlation between NHHR and the risk of hypertension. The higher NHHR levels increase hypertension risk, particularly among women, individuals with lower education levels, and non-Hispanic Black populations. There is a non-linear saturation effect observed between NHHR and hypertension. The incorporation of 3 machine learning models further elucidates the potential of interpretable machine learning in hypertension detection. As a potential biomarker for predicting hypertension risk, NHHR may play a key role in the prevention of hypertension, especially in the early identification, clinical assessment, and subsequent management of high-risk populations. Our findings emphasize the need for further exploration of the physiological mechanisms between NHHR and hypertension, as well as prospective longitudinal studies to validate their causal relationship. Additionally, it is essential to evaluate whether interventions targeting NHHR can effectively improve patient outcomes and clinical results, thereby clarifying its application potential in cardiovascular disease management.

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