Lipids in Health and Disease

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The joint and interactive effects of the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) and body mass index on the risk of depression, as well as the mediating role of NHHR: results from NHANES 2005–2023

Lingling Zhang[1], Yi Lai[2], Long Yan[2], Jiaping Fang[2] and Kai Wang[2*]

Abstract

Background Various research in the past has indicated that the NHHR, which represents the ratio of non-high-density lipoprotein cholesterol (non-HDL-C) to high-density lipoprotein cholesterol (HDL-C), and body mass index (BMI) each act independently as contributors to depression risk. Nonetheless, studies exploring the combination of NHHR with BMI in relation to depression are limited. Consequently, the central aim of this study is investigating the joint and interactive effects of NHHR and BMI on depression risk, as well as the mediating role of NHHR.

Methods Encompassing participants aged 20 years or over, this research incorporated a total of 39,704 individuals from the National Health and Nutrition Examination Survey (NHANES), which covered the period of 2005 to 2023. To analyze the impact of NHHR and its combination with BMI on depression, our analytical approach included multivariate logistic regression, restricted cubic spline modeling, interaction testing and subgroup analyses. Additionally, we studied the joint effects of NHHR and BMI. Finally, we applied a four-way decomposition analysis method to examine the interactions and mediating effects within the aforementioned relationships.

Results Among all participants in this study, the prevalence of depressive disorder (Patient Health Questionnaire-9 score ≥ 10) was 9.2%. Both the NHHR and BMI were associated with depression, which remained significant even after full adjustment for covariates [NHHR, OR (95% CI): 1.07 (1.04–1.09); BMI, OR (95% CI): 1.02 (1.02–1.03)]. Compared with the reference group, the OR (95% CI) for the highest groups of NHHR, BMI, and their product term NHHR-BMI were 1.41 (1.24–1.61), 1.35 (1.18–1.54), and 1.59 (1.37–1.84), respectively. Participants with NHHR in the fourth quartile and BMI exceeding 30 kg/m^2, had higher depression risk compared to other participants with NHHR in the first quartile and BMI below 25 kg/m^2 [OR (95% CI): 1.64 (1.34-2.00)]. Results of the four-way decomposition analyses indicated that

*Correspondence:
Kai Wang
kwemergency@163.com

Full list of author information is available at the end of the article

NHHR played a mediating role in the association between BMI and depression, with the mediating effect accounting for 17.6%. Similarly, NHHR also mediated 11.0% of the mediating effect between BMI and PHQ-9 score. However, no interaction between NHHR and BMI related to depression was found in the general population. After stratifying by gender, it was found that the mediated interaction between NHHR and BMI had a statistically significant effect on depression and PHQ-9 score in males.

Conclusions Depression risk is linked to both NHHR and BMI, and NHHR has a significant mediating impact on the association between BMI and depression. Notably, there is a non-negligible mediated interaction effect between BMI and NHHR in male participants. Compared to considering NHHR or BMI individually, participants had a higher risk of depression when the combined terms of the two were in the higher quartiles. These findings suggest that the combined assessment of these two indicators may help deepen the understanding and evaluation of depression, enhance the accuracy of risk stratification, and is worthy of further research.

Keywords NHHR, BMI, Depression, NHANES, Interaction, Mediation effect

Introduction

Currently, depression is becoming an increasingly significant global health issue. It is approximated that within a period of 12 months, 6% of the population are affected by depression, with a lifetime prevalence as high as 15–18%, indicating that depression is a common condition [1]. There is a systematic analysis that points out that depression is currently the top major reasons for disease burden across 204 countries and territories [2]. From 1990 to 2021, mental disorders, including depression, contributed to an increase in disability-adjusted life-years (DALYs) [2]. Furthermore, among mental disorders, depression is associated with the highest years lived with disability (YLDs) across all age groups [2]. Moreover, depression is reported by the World Health Organization as one of the top contributors to disability concerns on a worldwide basis. Specifically, the economic burden caused by major depressive disorder amounts to a staggering $326.2 billion annually in the U.S., which includes medical expenses, decreased work productivity, and other related costs [3]. Thus, identifying potential risk factors for depression through epidemiological research is extremely important for enhancing the therapy and prevention of depression.

As we know, the origins of depression are complex, involving various factors, including genetic, biochemical, environmental, and psychosocial elements. In general hospitals, as many as one-third of patients with depression may have underlying physical diseases [4]. These include diabetes, cardiovascular disease, chronic obstructive bronchitis, hypertension, metabolic disease, cancer, and so on [5–7]. Traditionally, the body mass index (BMI) has been an essential indicator for evaluating the extent of obesity, with higher BMI values indicating a more severe level of obesity. Some studies have shown that obese individuals may face an increased risk of having underlying diseases and are also more susceptible to depression [8, 9]. However, as a quick and simple clinical tool, BMI relies solely on weight and height to indirectly assess body shape, and it cannot reflect the body fat ratio, fat distribution, bone density, or muscle mass, which are its limitations [10]. As this situation evolves, there is a mounting enthusiasm for discovering indicators that can reveal more metabolic risks than BMI can reveal. In recent years, the NHHR has emerged as an innovative lipid combination index. Compared with conventional lipids indicators, the NHHR demonstrates exceptional efficacy for assessing the risk for cardiovascular diseases (CVD), diabetes, and metabolic disorders [11–13]. Previous research among U.S. adults has found that an increasing NHHR is correlated with a higher likelihood of depression, which is sufficient to illustrate the correlation between the two [14].

However, the interactions between NHHR, BMI and depression have not been sufficiently explored. Therefore, we carried out analyses built on the NHANES datasets spanning the period between 2005 and 2023 to probe the independent and joint effects of NHHR and BMI with depression, and to explore whether NHHR and BMI have any interactive effect on depression. Moreover, by examining the mediating effects of NHHR between BMI and depression, this study can reveal potential pathways for intervention. These results could offer healthcare professionals a new way to assess the risk of depression.

Methods

Study participants

The NHANES is a study project that includes a variety of surveys and questionnaires designed to assess health and lifestyle practices, as well as nutritional status of American citizens. The NHANES gathers various health and nutritional data from the American public using approaches of questionnaire surveys, physical examinations and lab tests, with the aim of obtaining epidemiological data on various diseases; analyzing basic demographic characteristics, nutritional status, and behavior patterns; and tracking the health trends and lifestyle changes of the population. This study utilized

NHANES data from cycles spanning the period 2005 through 2023. This survey covered 88,429 participants across these cycles. We excluded participants who under the age of 20 ($n = 37,208$). Those lacking records of the PHQ-9 (Patient Health Questionnaire-9) questionnaire ($n = 8,820$) or participants with missing NHHR data ($n = 2,331$) were also omitted from the analysis. Additionally, we excluded participants without BMI measurement results ($n = 366$) as shown in Fig. 1. Finally, the study sample consisted of 39,704 participants.

Assessment of depression symptoms

This study employs the PHQ-9 to determine whether participants are suffering from depression. The PHQ-9 is a questionnaire consisting of nine questions, aimed at screening depressive symptoms in primary healthcare and various medical environments, in addition to being utilized for quantifying the severity of depressive disorders [15, 16]. A score of 10 or above is generally considered as a possible indication of depression. According to the result of a previous study, the PHQ-9 has obvious advantages in diagnosis of depression (sensitivity: 88%, specificity: 85%) [17].

Assessment of NHHR

The NHHR is calculated employing the formula as follows: *[total cholesterol (TC)- HDL-C] / HDL-C*, and the unit of calculation is mg/dl [18]. Each participant was instructed by investigative staff to abstain from food for a minimum of 9 h before obtaining blood specimens in morning. These collected samples were aliquoted into vials frozen, and then sent to the laboratory. The concentrations of HDL-C and TC were determined utilizing enzymatic assay method with aid of the Roche Cobas 6000 chemistry analyzer (Roche Diagnostics Ltd., Basel, Switzerland).

Assessment of BMI

The formula to calculate BMI is *Weight (kg) / [Height (m)] ²*, with the result then rounded to a single decimal point. The measurements for body dimensions were gathered by skilled health professionals at the Mobile Examination Center (MEC).

Covariates

To conduct this study, we adjusted for several confounding factors as covariates. These involved sociodemographic characteristics, health conditions, and participants' living behaviors. The sociodemographic characteristics encompassed a spectrum of data, including age, gender (distinguished as female and male), and race, which was systematically categorized into five discrete classifications: mexican american, non-hispanic black, non-hispanic white, other Hispanic, and other race. The levels of education were split into two groups (high school or below, university or above), marriage status was sorted into three categorizations (never married, married/living with partner, widowed/divorced/separated), then income level was subsequently divided into two groups according to the poverty income ratio (PIR): less than 1, equal to or greater than 1. Lifestyle factors included self-reported daily activities, smoking, and drinking status. Daily activity levels were categorized as either moderate or vigorous, smoking status as never smoked, smoking at present, or smoking cessation, and drinking status as no / yes. Health status encompassed self-reported or clinically diagnosed diabetes, hypertension, and cardiovascular disease (CVD). Diabetes was identified by diabetes history as self-reported or a fasting blood glucose concentration reaching or exceeding 126 mg/dl. Hypertension was detected when systolic blood pressure (SBP) > 140 mmHg either diastolic blood pressure (DBP) > 90 mmHg during physical examination, or when there was a self-reported past incidence of hypertension. The CVD was diagnosed through participants' self-reported histories of cardiopathy or stroke. The questionnaire content regarding cardiopathy in NHANES included the following diseases: coronary artery disease, angina, heart failure and heart attack.

Statistical analysis

In this descriptive statistical study, all participants were classified into two categorizations: depressed and non-depressed, according to the scores from the PHQ-9 questionnaire. For the descriptive statistics of continuous variables, we used means and standard deviations (SD) to characterize their distribution characteristics. As for categorical variables, their data distribution was presented by proportion and frequency. For statistical comparisons of the baseline characteristics across categories, we used either T-tests or Chi-square tests. Among all participants, 4,599 (11.6% of the total 39,704) individuals had missing data (Supplementary Fig. 1). To more accurately represent the condition of the entire population, we employed the baseline characteristics for multiple imputation by chained equations for imputing missing data [19].

Since the use of stratified, clustered, and random sampling methods in the NHANES to select the sample, in order to guarantee that the results precisely reflect the situation of entire inhabitants, we considered sampling weights to weight the data for our study. We analyzed the associations among NHHR, BMI and depression risk in this study by constructing several multivariate logistic regression models, calculating the odds ratios (OR), also presenting the corresponding 95% confidence intervals (95% CI) of these connections. These multivariable logistic regression models include continuous variable models

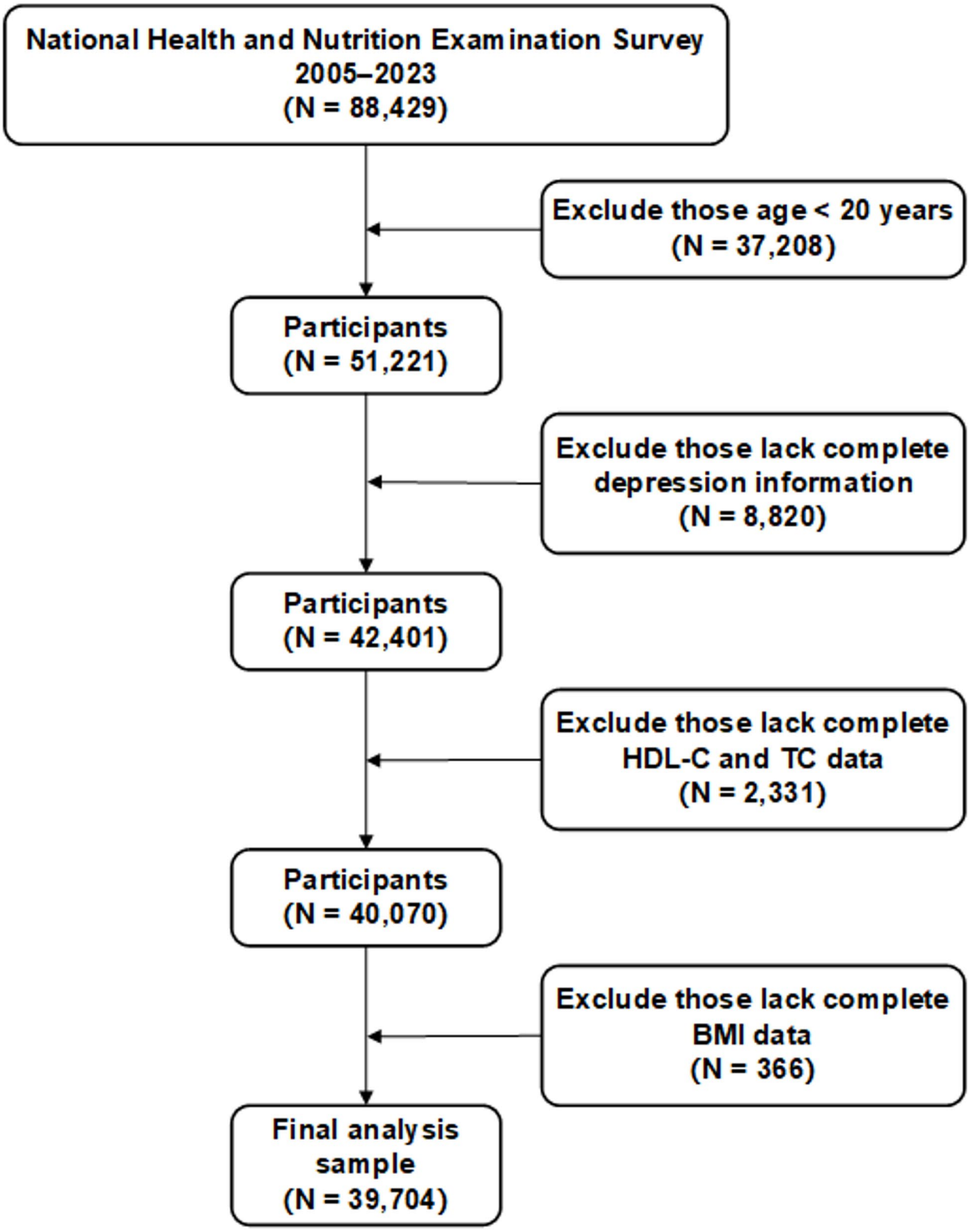

Fig. 1 Flowchart of the study participants
Legends: Abbreviations: HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; BMI: body mass index

and categorical variable models. Within the categorical models, the NHHR was divided into 4 levels according to quartile distribution, and the lowest level among them was taken as the reference. BMI was classified into 3 categories: below 25 kg/m² (reference group), 25–30 kg/m², and more than 30 kg/m². In addition, we included the product of the NHHR and BMI (NHHR-BMI) as a study variable, which was also segmented into quartiles. In the present study, three models were constructed for subsequent analyses. In Model 1, adjustments included age, gender, and racial characteristics. Model 2 was based on Model 1 and included additional variables such as education level, marriage status, PIR and daily activities for adjustments. Model 3 was built on Model 2, incorporating extra adjustments for smoking, drinking, hypertension, diabetes, as well as CVD. Additionally, we utilized 4 knots restricted cubic splines (RCS) for investigating the potential for non-linear relationships between variables. If the non-linear *p*-value of the RCS curve is less than 0.05, it indicates that the non-linear relationship within the model is statistically significant.

To evaluate the joint effect of NHHR and BMI with depression, participants were also categorized into 12 groups by NHHR (four quartiles) and BMI (three groups). These participants with lowest NHHR quartile and BMI below 25 kg/m² were used as the reference group, and we calculated the OR and 95% CI for depression in each group. Moreover, we also carried out subgroup analyses based on BMI subgroups in order to explore the connection between NHHR and depressive disorder, and to calculate the *p*-value of interaction.

Subsequently, we performed four-way decomposition analyses to quantify the interaction and mediation effects of NHHR in the association between BMI and depression. Introducing an advanced analytical framework, the four-way decomposition method refines the evaluation of exposure impacts by dissecting the total effect (TE) into four unique components: controlled direct effect (CDE), the direct effect without interaction and mediation; reference interaction (INTref), which solely encompasses interaction effects; mediated interaction (INTmed), which incorporating effects of both mediation and interaction; and pure indirect effect (PIE), concentrating exclusively on mediation without the influence of interaction [20]. This sophisticated approach offers a deeper insight into the nuanced relationships among variables, outperforming conventional metrics like relative excess risk due to interaction (RERI), attributable proportion (AP), synergy index (SI). Additionally, it addresses some shortcomings of conventional interaction analyses in the assessment of mediation effects, thus safeguarding against potential misestimations of the magnitude of clinical impacts. We used a directed acyclic graph (DAG) to illustrate the causal relationships between variables and drew a schematic diagram of the four-way decomposition to aid in understanding the distinctions among the various decomposed effects (Fig. 2). In the actual analysis, we established two models. In Model 1, the exposure was BMI, the mediator was NHHR, and the outcome was depression. In Model 2, the outcome variable becomes the PHQ-9 score. Each decomposition effect value bears a specific proportion to the total effect value, and this proportion can be negative (indicating a negative correlation). The sum of all effect values equals 100%, which can be expressed by the formula: $TE = CDE + INTref + INTmed + PIE$. The calculation method for the proportion of interaction effects is: $(INTref + INTmed)/ TE *100\%$. And the proportion of mediation effects is: $(PIE + INTmed)/ TE *100\%$ [20].

Finally, in an effort to validate the reliability and robustness of the research findings, various sensitivity analyses were carried out: (1) Analyzing the complete dataset without multiple imputation (included 35,105 participants); (2) Analyzing without considering sampling weights to avoid introducing additional computational errors; (3) Constructing Poisson regression models for analysis; (4) Calculating the E-value for quantifying the degree of correlation between unmeasured confounding factors and the results of observational studies. The E-value is a tool used to assess the impact of unmeasured confounding factors on study results. A higher E-value suggests that the study results are less influenced by unmeasured confounding factors, thereby enhancing the credibility of the findings [21]. Data calculations were accomplished using the statistical software R (version 4.4.0; Vienna, Austria). Data imputation was performed using the *mice* package in R software, with a total of 50 iterations conducted. And the four-way decomposition analyses were conducted using the med4way command in STATA (version 18.0; College Station, Texas, USA). In this study, if the p-value is < 0.05, it is considered that the result is adequately significant and possesses statistical significance.

Results

Baseline characteristics

During the 2005 to 2023 NHANES cycles, a total of 39,704 participants conformed to the inclusion standards for this cross-sectional study. Supplementary Table 1 describes a comparative analysis of baseline characteristics among the participants included versus those excluded. Among all the participants included in the study, 4,599 (11.6% of the total 39,704) had missing covariate data, including 22 for education level, 21 for marriage status, 3,583 for PIR, 145 for daily activities, 26 for smoking status, 38 for drinking status, 765 for diabetes disease, 3 for hypertension, and 169 for history of CVD. Supplementary Table 2 shows the differences in

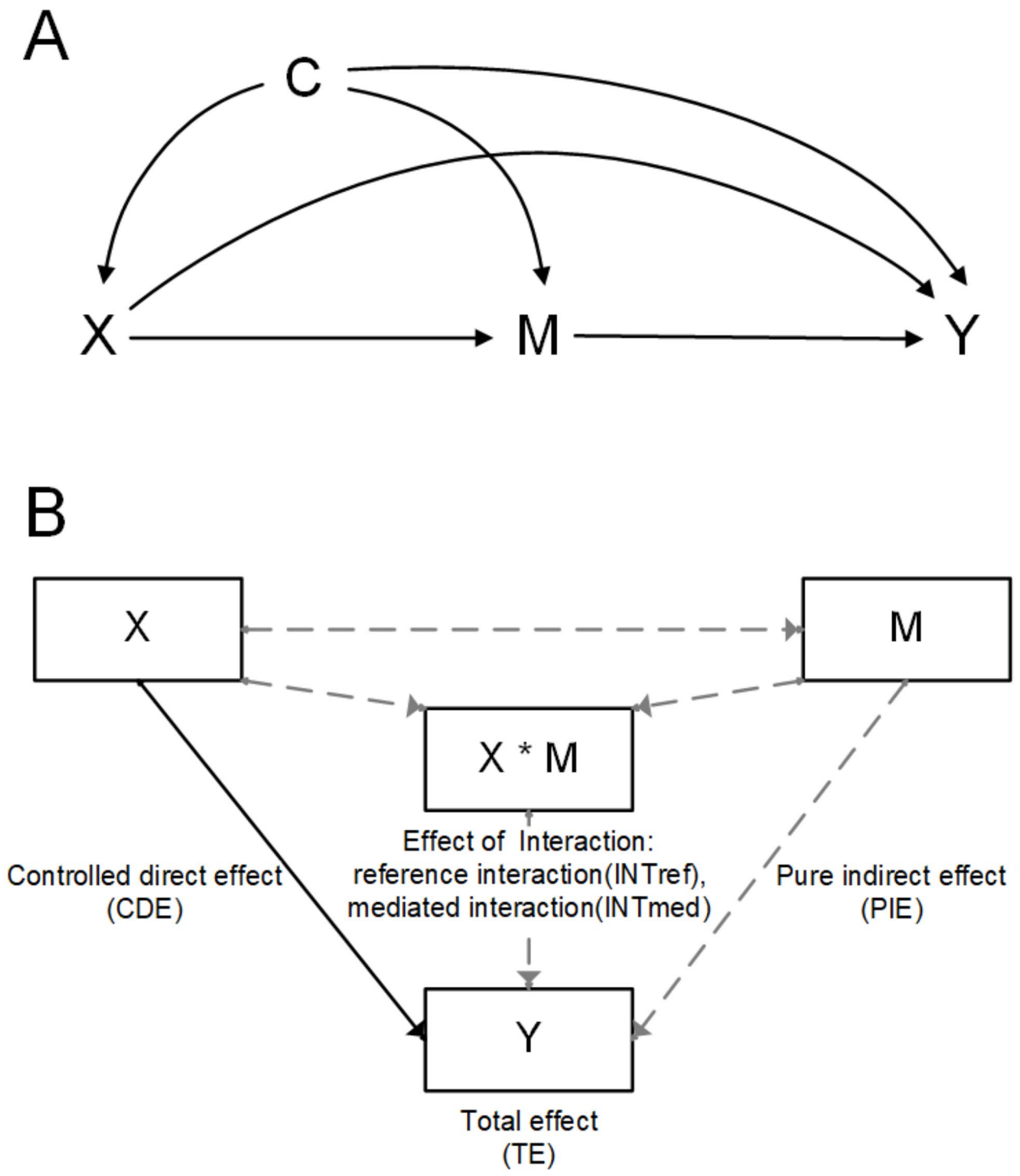

Fig. 2 Schematic representation of the interaction and mediation analysis framework
Legends: A, directed acyclic graph (DAG). B, four-way decomposition diagram. X, BMI as the exposure variable. M, NHHR as the mediator variable. Y, depression or PHQ-9 score as the outcome. C, covariate. X*M, interaction term between the independent variable and the mediator variable. Abbreviation: TE: total effect; CDE: controlled direct effect; INTref: reference interaction; INTmed: mediated interaction; PIE: pure indirect effect

baseline characteristics between participants with complete data and those with missing data.

Table 1 displays the participants' baseline characteristics categorized by whether they suffered from depressive disorder. In this study, 3,649 (9.2%) of the included participants were diagnosed as having depression (PHQ-9 score ≥ 10). The depressive participants, on average, were 48.90 years old (SD: 16.41). Those participants without

Table 1 Baseline characteristics of the participants based on depression status

Characteristic	Overall	PHQ-9 < 10	PHQ-9 ≥ 10	*P*-value[a]
	(*N* = 39,704)	(*N* = 36,055)	(*N* = 3,649)	
Age, years	50.09 (17.64)	50.21 (17.76)	48.90 (16.41)	< 0.001
Age group				< 0.001
20–44	16,169 (40.7%)	14,683 (40.7%)	1,486 (40.7%)	
45–65	14,427 (36.3%)	12,883 (35.7%)	1,544 (42.3%)	
> 65	9,108 (22.9%)	8,489 (23.5%)	619 (17.0%)	
Gender				< 0.001
Female	20,397 (51.0%)	18,077 (50.1%)	2,320 (63.6%)	
Male	19,307 (48.6%)	17,978 (49.9%)	1,329 (36.4%)	
Race				< 0.001
Mexican American	5,684 (14.3%)	5,188 (14.4%)	496 (13.6%)	
Non-Hispanic Black	7,967 (20.1%)	7,210 (20.0%)	757 (20.7%)	
Non-Hispanic White	17,951 (45.2%)	16,335 (45.3%)	1,616 (44.3%)	
Other Hispanic	3,891 (9.8%)	3,420 (9.5%)	471 (12.9%)	
Other Race	4,211 (10.6%)	3,902 (10.8%)	309 (8.5%)	
Education level[b]				< 0.001
High school or below	17,689 (44.6%)	15,658 (43.5%)	2,031 (55.7%)	
University or above	21,993 (55.4%)	20,377 (56.5%)	1,616 (44.3%)	
Marriage status[b]				< 0.001
Never married	4,922 (12.4%)	4,431 (12.3%)	491 (13.5%)	
Married/Living with partner	23,578 (59.4%)	21,377 (60.9%)	1,627 (44.6%)	
Widowed/Divorced/Separated	11,183 (28.2%)	9,655 (26.8%)	1,528 (41.9%)	
PIR[b]				< 0.001
< 1	7,052 (19.5%)	5,883 (17.9%)	1,169 (35.5%)	
≥ 1	29,069 (80.5%)	26,942 (82.1%)	2,127 (64.5%)	
Daily activities[b]				< 0.001
Moderate	25,544 (64.3%)	22,943 (63.8%)	2,601 (71.7%)	
Vigorous	14,015 (35.4%)	12,990 (36.2%)	1,025 (28.3%)	
Smoking status[b]				< 0.001
Never	22,239 (56.0%)	20,669 (57.4%)	1,570 (43.0%)	
Smoking at present	7,626 (19.2%)	6,385 (17.7%)	1,241 (34.0%)	
Smoking cessation	9,813 (24.7%)	8,977 (24.9%)	836 (22.9%)	
Drinking status[b]				0.314
No	8,903 (22.4%)	8,110 (22.5%)	793 (21.8%)	
Yes	30,763 (77.6%)	27,913 (77.5%)	2,850 (78.2%)	
Diabetes[b]				< 0.001
No	32,274 (82.9%)	29,588 (83.6%)	2,686 (75.3%)	
Yes	6,665 (17.1%)	5,786 (16.4%)	879 (24.7%)	
Hypertension[b]				< 0.001
No	21,502 (54.2%)	19,778 (54.9%)	1,724 (47.2%)	
Yes	18,199 (45.8%)	16,274 (45.1%)	1,925 (52.8%)	
CVD[b]				< 0.001
No	35,219 (89.1%)	32,280 (89.9%)	2,939 (81.3%)	
Yes	4,316 (10.9%)	3,638 (10.1%)	678 (18.7%)	
BMI, kg/m^2	29.42 (7.05)	29.25 (6.87)	31.19 (8.38)	< 0.001
BMI group				< 0.001
< 25	10,951 (27.6%)	10,097 (28.0%)	854 (23.4%)	
25–30	13,284 (33.5%)	12,296 (34.1%)	988 (27.1%)	
> 30	15,469 (38.9%)	13,662 (37.9%)	1,807 (49.5%)	
TC, mg/dl	192.08 (42.12)	191.94 (41.85)	193.48 (44.68)	0.035
HDL-C, mg/dl	53.37 (16.08)	53.53 (16.10)	51.75 (15.82)	< 0.001
NHHR	2.88 (1.41)	2.86 (1.40)	3.04 (1.56)	< 0.001
Q1 (0.28–1.89)	9,933 (25.0%)	9,140 (25.4%)	793 (21.7%)	

Table 1 (continued)

Characteristic	Overall (*N* = 39,704)	PHQ-9 < 10 (*N* = 36,055)	PHQ-9 ≥ 10 (*N* = 3,649)	*P*-value[a]
Q2 (1.90–2.61)	10,003 (25.2%)	9,160 (25.4%)	843 (23.1%)	
Q3 (2.62–3.55)	9,853 (24.8%)	8,878 (24.6%)	975 (26.7%)	
Q4 (3.56-27.00)	9,915 (25.0%)	8,877 (24.6%)	1,038 (28.4%)	
NHHR-BMI[c]	86.82 (51.22)	85.79 (50.18)	97.00 (59.66)	< 0.001
Q1 (8.00-50.48)	9,929 (25.0%)	9,194 (25.5%)	735 (20.1%)	
Q2 (50.49–76.33)	9,925 (25.0%)	9,152 (25.4%)	773 (21.2%)	
Q3 (76.34-111.06)	9,924 (25.0%)	8,950 (24.8%)	974 (26.7%)	
Q4 (111.07-922.78)	9,926 (25.0%)	8,759 (24.3%)	1,167 (32.0%)	

[a] *P*-value was calculated by T-test or Chi-square test where appropriate

[b] Missing data: 22 for education level, 21 for marriage status, 3,583 for PIR, 145 for daily activities, 26 for smoking status, 38 for drinking status, 765 for diabetes disease, 3 for hypertension, 169 for history of CVD

[c] The NHHR-BMI was the product of NHHR and BMI

Mean (SD) was used to describe continuous variables, proportions were used to describe categorical variables

Abbreviations: PHQ-9: Patient Health Questionnaire 9; PIR: poverty income ratio; CVD: Cardiovascular disease; BMI: body mass index; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; NHHR: non-high-density lipoprotein cholesterol (non-HDL-C) to high-density lipoprotein cholesterol (HDL-C) ratio

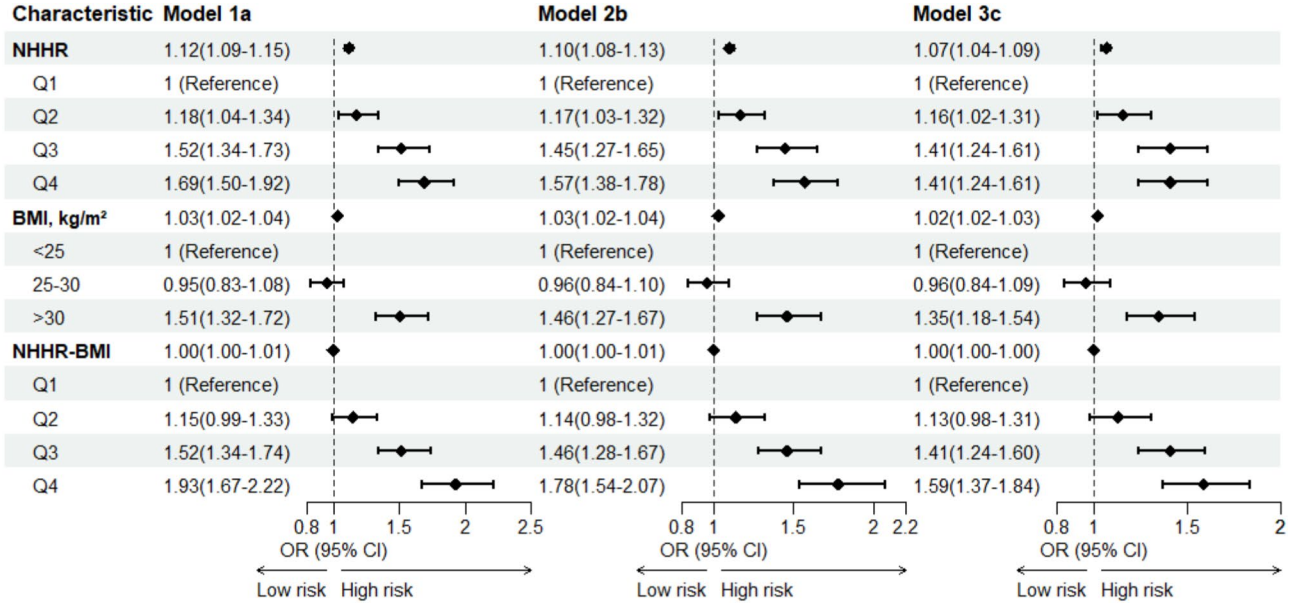

Fig. 3 Associations of NHHR and BMI with depression

Legends: a Model 1 adjusted for demographic factors including age, gender, race. b Model 2 adjusted for age, gender, race, education level, marriage status, PIR, daily activities. c Model 3 as model 2 plus smoking status, drinking status, hypertension, diabetes, CVD. Abbreviations: NHHR: non-high-density lipoprotein cholesterol (non-HDL-C) to high-density lipoprotein cholesterol (HDL-C) ratio; Q, quartile; BMI: body mass index; NHHR-BMI: calculated by multiplying NHHR by BMI; OR: odds ratio; CI: confidence interval; PIR: poverty income ratio; CVD: cardiovascular disease

depressive symptoms averaged 50.21 (SD: 17.76) years in age. Compared with individuals without depression, depressed individuals exhibited significantly more elevated levels of NHHR and BMI, with the average NHHR being 3.04 (SD: 1.56) and the average BMI being 31.19 (SD: 8.38) kg/m². It was observed that depressed participants had an enhanced probability of being female; having BMI over 30 kg/m²; being widowed, divorced, or separated marital status; not having received university education; having a lower poverty income ratio; being inactive in daily activities; currently smoking; having increased incidence rates of diabetes, hypertension, and CVD; and having lower HDL-C and higher TC concentrations. Supplementary Table 3 and Supplementary Table 4 show the participants' characteristics based on NHHR and BMI groups, respectively.

Associations of NHHR and BMI with depression

Figure 3 shows the relationships among NHHR, BMI, and incidence of depression. After all confounding covariates were adjusted within Model 3, weighted logistic regression analyses disclosed that a continuous

increase in NHHR was directly linked to depression with an OR of 1.07, and the 95% CI was 1.04 to 1.09 ($P < 0.001$). Compared with quartile 1 of NHHR, the remaining quartiles of NHHR were significantly associated with heightened depression risk, with the OR (95% CI) for depression being 1.41 (1.24 to 1.61) for quartile 4. Similarly, as BMI increased by one unit, the depression risk correspondingly rose with the OR (95% CI) of 1.02 (1.02 to 1.03) and the *P*-value < 0.001. Participants whose BMI fell into the top level exhibited greater incidence of depression compared to other participants who had the minimum BMI level, with OR (95% CI) of 1.35 (1.18 to 1.54) and the *P*-value < 0.001. Additionally, we also included the product of NHHR and BMI (NHHR-BMI) as a study variable, and a significant association was discovered between the NHHR-BMI and depression risk. Specifically, individuals with the top quartile of NHHR-BMI were related to an increased odds ratio for depressive symptoms, with OR (95% CI) of 1.59 (1.37 to 1.84) and the *P*-value < 0.001. All of the above results showed a significant trend with $P < 0.001$ (Supplementary Tables 5–7). We subsequently conducted RCS analyses, which indicated that both NHHR and NHHR-BMI were positively and nonlinearly associated with depression (Fig. 4). Meanwhile, it was found that there exists a U-shaped nonlinear connection between BMI and depression.

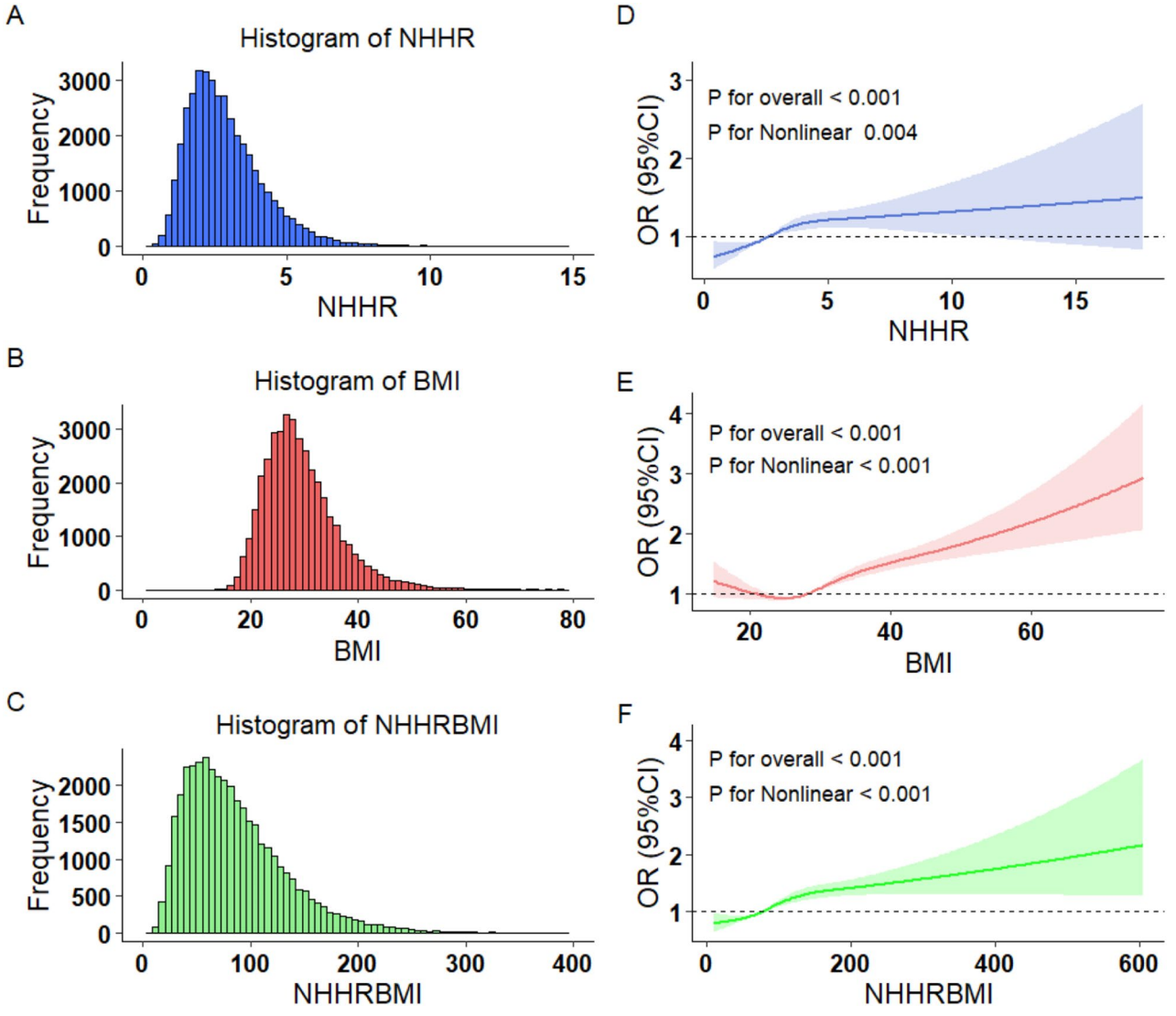

Fig. 4 Nonlinear associations of NHHR and BMI with depression

Legends: A, B, C Distribution for NHHR, BMI and NHHR-BMI; D, E, F Restricted cubic splines of the associations between NHHR/ BMI/ NHHR-BMI and depression. All models were adjusted for age, gender, race, education level, marriage status, PIR, daily activities smoking status, drinking status, hypertension, diabetes and CVD. Abbreviation: NHHR: non-high-density lipoprotein cholesterol (non-HDL-C) to high-density lipoprotein cholesterol (HDL-C) ratio; BMI: body mass index; NHHR-BMI: calculated by multiplying NHHR by BMI; OR: odds ratio; CI: confidence interval; PIR: poverty income ratio; CVD: cardiovascular disease

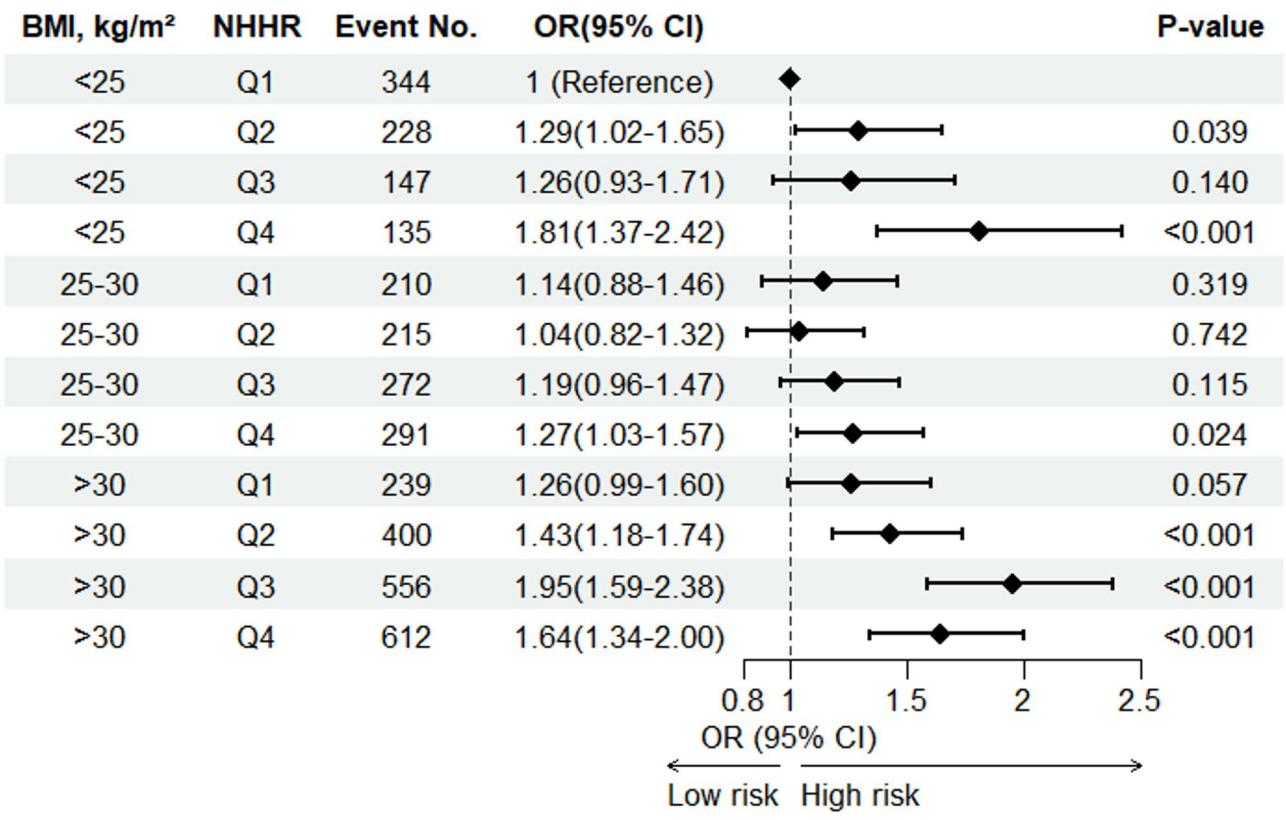

Fig. 5 Joint associations of NHHR and BMI with depression in fully adjusted model

Legends: The model was adjusted for age, gender, race, education level, marriage status, PIR, daily activities smoking status, drinking status, hypertension, diabetes and CVD. Abbreviation: BMI: body mass index; NHHR: non-high-density lipoprotein cholesterol (non-HDL-C) to high-density lipoprotein cholesterol (HDL-C) ratio; OR: odds ratio; CI: confidence interval; PIR: poverty income ratio; CVD: cardiovascular disease

Table 2 Four-way decomposition of the association between BMI and depression mediated by NHHR

Effect	Estimates (95% CI)	*P*-value	Proportion
TE	0.199 (0.152–0.245)	< 0.001	100%
CDE	0.162 (0.116–0.208)	< 0.001	81.4%
INTref	0.002 (-0.003-0.008)	0.382	1.0%
INTmed	0.007 (-0.004-0.017)	0.240	3.5%
PIE	0.028 (0.016–0.040)	< 0.001	14.1%

Model was adjusted for age, gender, race, education level, marriage status, PIR, daily activities smoking status, drinking status, hypertension, diabetes and CVD

Abbreviations: NHHR: non-high-density lipoprotein cholesterol (non-HDL-C) to high-density lipoprotein cholesterol (HDL-C) ratio; BMI: body mass index; CI, confidence interval; TE: total effect; CDE: controlled direct effect; INTref: reference interaction; INTmed: mediated interaction; PIE: pure indirect effect; PIR: poverty income ratio; CVD: cardiovascular disease

Joint effects of NHHR and BMI on depression

We categorized participants into 12 groups based on NHHR (four quartiles) and BMI (three categories) for joint analyses. Figure 5 shows that participants with BMI exceeding 30 kg/m² and in the fourth quartile of NHHR exhibit OR (95% CI) of 1.64 (1.34 to 2.00) with statistical significance of *P*-value < 0.001 for depression, in comparison to participants who have BMI of less than 25 kg/m² and in the lowest NHHR quartile. Subgroup analyses based on the three BMI categories revealed a *P*-value for interaction of 0.073 (Supplementary Table 8).

Interactive and mediating roles of NHHR and BMI on depression

Table 2 presents the results of the four-way decomposition analysis examining the interaction and mediating effects of NHHR on the association between BMI and depression, with adjustments for all confounding factors, considering both direct and indirect pathways. The results show that the total effect (TE) of BMI on depression is predominantly direct and significant, with the controlled direct effect (CDE) accounting for 81.4%, which remains significant even after adjusting for multiple covariates. The pure indirect effect (PIE) mediated by NHHR accounts for 14.1% ($P < 0.001$), with the total proportion of the mediated effect reaching 17.6%, of which INTmed accounts for 3.5%. However, the reference interaction (INTref) and mediated interaction (INTmed) are not significant enough ($P > 0.05$). It can be concluded that NHHR plays an undeniable mediating role in the association between BMI and depression, but there is no significant interaction effect. Table 3 demonstrates the four-way decomposition analysis of the association between BMI

Table 3 Four-way decomposition of the association between BMI and PHQ-9 score mediated by NHHR

Effect	Estimates (95% CI)	*P*-value	Proportion
TE	0.427 (0.376–0.478)	< 0.001	100%
CDE	0.378 (0.326–0.431)	< 0.001	88.5%
INTref	0.002 (0.000-0.003)	0.105	0.5%
INTmed	0.012 (-0.002-0.026)	0.091	2.8%
PIE	0.035 (0.020–0.049)	< 0.001	8.2%

Model was adjusted for age, gender, race, education level, marriage status, PIR, daily activities smoking status, drinking status, hypertension, diabetes and CVD

Abbreviations: NHHR: non-high-density lipoprotein cholesterol (non-HDL-C) to high-density lipoprotein cholesterol (HDL-C) ratio; BMI: body mass index; PHQ-9: Patient Health Questionnaire 9; CI, confidence interval; TE: total effect; CDE: controlled direct effect; INTref: reference interaction; INTmed: mediated interaction; PIE: pure indirect effect; PIR: poverty income ratio; CVD: cardiovascular disease

and PHQ-9 score, mediated by NHHR. BMI has a significant impact on the PHQ-9 score, with the direct effect still accounting for the majority of the total effect, the CDE representing 88.5%. NHHR plays a sufficiently noteworthy role in the association between BMI and PHQ-9 score through a PIE, accounting for 8.2%, which is statistically significant ($P < 0.001$). Including INTmed, NHHR mediated a total of 11.0% of the total effect size in this process. Similar to depression, when PHQ-9 score is used as the outcome variable, the INTref and INTmed between BMI and NHHR did not show significant statistical significance ($P > 0.05$). Overall, the impact of BMI on depression and PHQ-9 scores is primarily realized through direct effects, while NHHR exerts some influence on this relationship through mediating mechanisms. Future research can further explore the specific mechanisms of NHHR as a mediating variable.

Subgroup and sensitivity analyses

Supplementary Tables 9–14 display the results stratified by age and gender groups. It can be observed that among participants under the age of 65 and female participants, the PIE of NHHR in the relationship between BMI and depression or PHQ-9 are relatively significant ($P < 0.001$), showing a more pronounced mediating effect, but there is no obvious interaction (Supplementary Tables 11–13). Compared with younger participants, participants over the age of 65 had a higher proportion of NHHR mediation in the association between BMI and depression, reaching 21.3% (Supplementary Table 12). The proportion of NHHR's mediating effect is relatively stable across different age groups and among females when PHQ-9 score is used as the outcome variable. However, unlike female participants, among male participants, with the exception of CDE, the INTmed of NHHR accounted for a larger proportion and showed statistical significance ($P < 0.05$) in both models, with the proportions being 20.2% and 13.2% respectively (Supplementary Table 14). These findings indicate that males and females may exhibit distinct patterns in the association between these two factors and depression. Specifically, the mediated interaction between NHHR and BMI appears to have a more pronounced effect on depression in males; whereas in females, NHHR exerts a more significant influence on the association between BMI and depression through mediating mechanisms.

The E-value calculation shows a strong correlation between NHHR and BMI with depression (Supplementary Table 15). Supplementary Tables 16–21 list the results of sensitivity analyses, indicating that multiple imputation and weighted analysis do not affect the reliability of the results. Furthermore, the use of Poisson regression models reveals that the results remain equally robust.

Discussion

Based on our knowledge, this appears to be the inaugural research endeavor to investigate the relationship among NHHR, BMI, and depression within samples that reflect the demographic makeup of the U.S. population. We discovered that increased NHHR or BMI each correlates with a greater likelihood of experiencing depression, exhibiting a non-linear relationship within this nationwide cross-sectional study. After adjusting for all covariates, the observed trend remained statistically significant. In joint analyses, the combination or product of NHHR and BMI showed a significantly increased correlation with the risk of depression compared to independent indicators, and it was more favorable for predicting the occurrence of depression.

It can be noted from previous studies that there is a link between BMI (or obesity) and the likelihood of depression. Consistent with our own results, some research has revealed that BMI is associated with depression in a U-shaped pattern, indicating a nonlinear correlation [22–25]. Likewise, the Canadian Community Health Surveys (CCHS) study, the German population study, the Health Study of Trøndelag (HUNT) in Norway, and the Taiwan Biobank Study have shown that individuals with excess weight or obesity have a higher tendency to suffer from depression [26–29]. Several studies employing Mendelian randomization with genetic variants corroborated the previously mentioned findings [30–32]. In addition, numerous cohort studies have confirmed that BMI serves as a known risk element for various health issues, including CVD, diabetes, metabolic disorders, and cancer [33–36]. This may be closely associated with metabolic abnormalities caused by an increase in BMI and even obesity, including atherosclerosis, insulin resistance, reproductive endocrine disorders, oxidative stress and chronic inflammation, etc [37–39]. These pathological mechanisms all have adverse effects on individual mental health, promoting the onset of depression.

On the other hand, metabolic abnormalities not only manifest as obesity but also often coexist with dyslipidemia. Earlier research has confirmed that metabolic syndrome can lead to elevated triglycerides (TG), reduced HDL, as well as increased low-density lipoprotein (LDL) concentrations [40, 41]. The National Cholesterol Education Program issued the Adult Treatment Panel (ATP) III guidelines in 2001, wherein the concept of non-HDL-C was formally introduced for the first time and established as one of the targets for lipid management [42]. Non-HDL-C represents the combined cholesterol levels in various lipoprotein particles, including LDL-C, lipoprotein(a), triglyceride-rich lipoproteins (TRL), and TRL remnants, without HDL-C. The estimated value of Non-HDL-C can be approximated by subtracting HDL-C concentration from TC concentration. Several research in the past has revealed the correlation between depression and HDL-C or non-HDL-C, but results are not entirely consistent. A retrospective observational study conducted among the Welsh population indicated that depressive patients have a lower likelihood of achieving the non-HDL-C target being recommended in accordance with the ESC/EAS Guidelines [43]. A study using NHANES data showed a positive connection involving non-HDL-C along with depression risk, presenting adjusted OR(95% CI) of 1.22 (1.03–1.45) [44]. Another study using murine model of chronic social defeat stress (CSDS), which exhibits chronic stress and mimics the symptoms observed in depression as well as post-traumatic stress disorder, also found similar conclusions [45]. A meta-analysis of 11 case-control research demonstrated a significant correlation between reduced HDL-C concentrations and first episode of depression [46]. Additionally, a population-based study utilizing the Apolipoprotein-Related Mortality Risk (AMORIS) cohort, which involved 211,200 participants, showed the opposite correlation between HDL-C levels and depressive disorders [47]. Nevertheless, there are a few studies that have drawn different results, and some even contradicted the aforementioned findings. For instance, the Multi-Ethnic Study of Atherosclerosis (MESA) cohort has demonstrated that reduced initial non-HDL-C concentrations was significantly correlated with increased likelihood of developing depression [48]. Likewise, research conducted with adolescents from a children's hospital in Toronto indicated that greater severity of depressive symptoms was correlated with higher levels of HDL-C [49]. Factors contributing to these differing results could be differences in participant count, age, gender, racial backgrounds, and approaches to evaluating depressive symptoms. Hence, it is necessary to search for new lipid biomarkers to deepen our understanding between lipid metabolism and depression.

Recently, a novel metric named the NHHR index has been proposed as the division of non-HDL-C by HDL-C. NHHR offers numerous benefits over conventional lipid biomarkers, notably in its stronger associations with conditions such as cardiovascular diseases, diabetes, cancers, and others [12, 50, 51]. Although previous findings have confirmed the distinct advantages of NHHR, investigations into the correlation between NHHR and depressive disorders are yet to be thoroughly explored. Currently, only three studies utilizing NHANES data can be retrieved. One of these studies noticed direct relationship between NHHR and depression among adult Americans, with a direct proportionality observed [14]. The subsequent research showed that increased NHHR is associated with elevated post-stroke depression (PSD) risk [52]. The last study indicated that NHHR partially mediated the correlation between depression and infertility among female individuals in America, with NHHR also being positively linked to the degree of depression [53]. Therefore, we conducted this study for exploring the relationship among NHHR, BMI and depression, as well as investigating whether there are any interactive or mediating effects.

We know that dyslipidemia and BMI are both risk factors for metabolic diseases, and metabolically disordered individuals have significantly increased risk for developing depression [54–57]. On the one hand, obesity and dyslipidemia are not independent of each other; there is a malignant and complementary relationship between these two conditions. When obesity occurs, the overexpansion of fat cells and the excessive accumulation of fat tissue can promote adiposopathy, leading to abnormal circulating lipids. The most common manifestations are hypertriglyceridemia and reduced HDL-C concentrations [58]. On the other hand, lipoprotein abnormalities, particularly the deficiency of HDL-C as well as the increase of small and dense non-HDL-C, disrupt lipid metabolism. This disruption can lead to enhanced fat tissue formation and reduced breakdown, which in turn makes the development of an obese physique more likely [59, 60]. Currently, there are several hypotheses regarding the biological mechanisms underlying depression, including chronic inflammation, neurotransmitter imbalance, hypothalamus-pituitary-adrenal (HPA) axis dysfunction, impaired neuroplasticity, oxidative stress, alterations in the gut microbiome composition, genetic factors, and others [61–64]. In a physiological state, HDL-C not only scavenges circulating endotoxins but also inhibits the maturation and activation processes of macrophages and other antigen-presenting cells (APCs), suppressing inflammatory signaling, thereby alleviating inflammatory stress [65]. During obesity, the body abnormally releases an abundance of cytokines that promote inflammation, including interleukin-6 (IL-6) and

tumor necrosis factor-α (TNF-α), while simultaneously decreases the synthesis of anti-inflammatory factors like adiponectin and so on [66]. These cytokines may affect the biosynthesis and metabolism of neurotransmitters, especially gamma-aminobutyric acid (GABA) and serotonin (5-HT), as well as dopamine (DA), as they play a key role in mood regulation [67, 68]. Lower levels of HDL-C contribute to these chronic inflammatory effects [69, 70]. Current evidence indicates a connection between depression and dysregulation of the HPA axis [71]. Individuals with obesity and dyslipidemia show heightened HPA axis activity, which leads to higher cortisol concentrations. High concentrations of cortisol can damage neurons within the hippocampus; furthermore such damage is closely linked with the onset of depression [72]. Similarly, these patients often experience insulin resistance. Insulin not only regulates blood glucose but also participates in synapse formation in the brain, enhancing neuronal plasticity and contributing to neuronal survival [73]. Insulin resistance might result in dysfunctional insulin signaling pathways within brain, thereby elevating the risk of depression [74]. When metabolic abnormalities occur, mitochondrial function is impaired, affecting the energy supply to neurons, leading to abnormal synthesis and secretion of neurotransmitters [75]. Moreover, mitochondrial dysfunction can increase oxidative stress, which can damage neurons and subsequently affect the normal functioning of the brain [76]. A growing amount of evidence points out that the imbalance of gut microbiota is involved within pathophysiological mechanisms underlying depression, a viewpoint supported by a study in the Netherlands population [64]. The gut-brain axis might illustrate the manner in which this imbalance affects brain function. Specifically, variations in gut microbes' generation of short-chain fatty acids (SCFAs) can alter neurotransmitter equilibrium and inflammatory responses, consequently affecting mood and behavior [77]. Moreover, existing literature has confirmed a close correlation between dyslipidemia, obesity, and gut microbiota [78].

From the above evidence, it can be observed that the biological mechanisms among obesity, dyslipidemia, and depression are multifaceted. Understanding these mechanisms can aid in finding more effective methods of prevention and treatment. Therefore, we conducted this study with the aim of exploring the correlations among NHHR, BMI, and depression, while also searching for possible interactive and mediating effects. Our research results confirm that NHHR and BMI are significantly correlated with depression risk, and that the combination or product of NHHR and BMI can enhance this association, providing better identification of the presence of depression.

Strengths and limitations

Here are numerous advantages of our study. Following are some of them: Firstly, we utilized an extensive, nationally representative sample with weights, which better reflects the characteristics of U.S. adults. Secondly, we incorporated the latest data from the NHANES 2005–2023 cycle into study to enhance the credibility of our research and accurately reflect the true epidemiological characteristics of the disease. Thirdly, BMI and NHHR indices do not require fasting, are easy to obtain, and involve simple calculations, making them widely applicable. In addition, we controlled for potential confounders, adjusted for covariates, designed multivariate regression models, and finally employed various sensitivity analyses to substantiate the validity and robustness of the results. Of course, there also possesses some limitations that are worth noting simultaneously. First of all, the cross-sectional nature of the study design restricts our ability to establish causal relationships, representing a significant limitation of the research. Secondly, this study didn't incorporate populations from countries outside the U.S., as it is well-known that there are considerable variations exist in the incidence of depression and blood lipid levels across different countries and regions [79, 80]. Thirdly, to increase the sample size of the study, we used data spanning a longer period of time and did not consider the impact of the COVID-19 pandemic. Results from prior studies have revealed that the prevalence of depressive disorders is on the rise annually, and using data from different years may introduce errors into our findings [81, 82]. Moreover, depressive symptoms in this study were self-reported. Although the PHQ-9 questionnaire is highly effective in identifying symptoms of depression, it cannot be used as a diagnostic criterion for depression, and substantial evidence suggests that the results from the questionnaire may be biased [83].

Conclusion

The results showed that NHHR and BMI exhibit significant nonlinear associations with depression risk within both their joint and product terms. Multivariate logistic regression indicated that, compared to considering NHHR or BMI individually, participants had a higher risk of depression when the combined terms of the two were in the higher quartiles. Additionally, NHHR partially mediated the association between BMI and depression. No interaction between NHHR and BMI related to depression was found in the general population. However, after stratifying by gender, it was found that the mediated interaction between NHHR and BMI had a statistically significant effect on depression in males. These results suggest that BMI and blood lipids are key factors in the management of depression risk, the combined assessment of NHHR and BMI may help deepen

the understanding and evaluation of depression. Our research yields useful insights into identifying depression, which is of great significance and warrants further research to explore the potential pathophysiological mechanisms involved.

Abbreviations

Non-HDL-C	Non-high-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
NHHR	Non-HDL-C to HDL-C ratio
BMI	Body mass index
NHANES	National Health and Nutrition Examination Survey
RCS	Restricted cubic spline
NHHR-BMI	Product of NHHR and BMI
NHHR + BMI	Combination of NHHR and BMI
PHQ-9	Patient Health Questionnaire-9
TC	Total cholesterol
PIR	Poverty income ratio
CVD	Cardiovascular disease
TG	Triglyceride
LDL-C	Low-density lipoprotein cholesterol
TE	Total effect
CDE	Controlled direct effect
INTref	Reference interaction
INTmed	Mediated interaction
PIE	Pure indirect effect

Supplementary Information

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Supplementary Material 1

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Author contributions

LLZ was responsible for conceiving and designing this study, conducting statistical analyses, also drafting the manuscript; YL offered statistical support and helped shape the conceptualization and methodology of this study; LY and JPF took part in collecting and analyzing the dataset, as well as creating figures; KW scrutinized, revised the final edition of manuscript. Each author has certified that this manuscript accurately reflects the research conducted and that all content is complete.

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Data availability

The datasets utilized in this research were publicly available and can be accessed via this website: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

Declarations

Ethics approval and consent to participate

The NHANES protocols have been reviewed and approved by the Ethics Review Board of the National Center for Health Statistics (NCHS), and every participant has signed an informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Clinical Laboratory, The First People's Hospital of Xiaoshan District, Xiaoshan Affiliated Hospital of Wenzhou Medical University, Hangzhou 311200, Zhejiang, China
[2]Department of Emergency, The First People's Hospital of Xiaoshan District, Xiaoshan Affiliated Hospital of Wenzhou Medical University, Hangzhou 311200, Zhejiang, China

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