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# Study on the relationship between the non-HDL/HDL cholesterol ratio (NHHR) and endometriosis: a cross-sectional analysis utilizing the NHANES dataset

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## Abstract

**Background** Numerous previous studies have suggested dyslipidemia is possibly linked to endometriosis (EMs). The connection between endometriosis and NHHR remains largely unexplored. Thus, this investigation examined whether NHHR is correlated with endometriosis development among adult women in the United States of America.

**Methods** Data from the 1999–2006 National Health and Nutrition Examination Survey (NHANES) were analyzed in a cross-sectional study, with a final sample of 4,990 participants. To investigate the potential association between NHHR and the likelihood of developing endometriosis, we employed two statistical models: a weighted multivariate logistic regression model and a restricted cubic spline model. Data visualization included scatter plots with locally estimated scatterplot smoothing (LOESS) curves to illustrate the relationship between NHHR and the probability of endometriosis. To ensure the reliability of our findings, we subsequently conducted subgroup analyses and interaction tests to assess their stability.

**Results** In this study, after accounting for all potential confounders, it was found that for every one-point elevation in NHHR, the risk of developing endometriosis increased by 17% (95% CI: 1.05–1.35, $p = 0.04$). A linear dose-response association was identified that connected NHHR with the risk of endometriosis (P for nonlinear = 0.1315). Interaction results from subgroup analyses suggested that an association between NHHR and risk of endometriosis was largely unaffected by race, educational background, or marital status, among others.

**Conclusion** NHHR and the probability of developing endometriosis are significantly correlated in the U.S. population, suggesting that further research on NHHR could assist in non-invasive diagnosis of endometriosis.

**Keywords** NHHR, Lipid ratios, NHANES, Endometriosis, Cross-sectional study

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## Introduction

Endometriosis (EMs) represents a prevalent gynecological disorder marked by the existence of active, estrogen-sensitive endometrioid glands and stromal tissue located external to the uterine cavity [1], and the primary manifestations of this condition encompass menstrual cramps, persistent pelvic discomfort, and impaired fertility, all of which notably diminish the patients' quality of life and increase their financial burden [2]. Based on the demographic projections provided by the World Bank for 2017, it affects about 190 million women globally [3]. Diagnosing endometriosis presents notable difficulty due to the broad spectrum of manifestations exhibited and lack of specificity. Although ultrasound has a sensitivity exceeding 90% and provides typical visualization [4], it is limited in detecting superficial endometriosis in women [5]. Even the gold standard of laparoscopic-guided biopsy may result in a diagnostic delay of 6 to 11 years [6–8]. Therefore, the advancement of novel, non-intrusive approaches and predictive blood biomarkers to enable early prediction of endometriosis is essential.

While the etiology of endometriosis is understood to be multifactorial, involving inflammatory responses, oxidative stress, immune dysfunction, metabolic processes, and genetic factors, its pathogenesis remains incompletely elucidated. Research has demonstrated that endometriosis and atherosclerosis exhibit comparable pathogenesis with regard to oxidative stress and inflammatory markers [9]. Alterations in lipid metabolism, particularly abnormal blood lipid levels, could foster disease development via influencing redox balance and inflammation [10]. However, the link between endometriosis and lipid metabolic processes has previously been controversial. A cross-sectional study [11] reported a correlation between endometriosis and elevated triglycerides (TG) along with low-density lipoprotein cholesterol (LDL-C). Alternatively, a different prospective investigation [12] revealed an insignificant correlation between endometriosis and TG levels, along with an inverse relationship with LDL-C concentrations. Retrospective analysis [13] found that in comparison to normal subjects, individuals with endometriosis exhibited elevated serum concentrations of high-density lipoprotein cholesterol (HDL-C). Research has demonstrated that female patients suffering from endometriosis exhibit a lipid profile conducive to the progression of atherosclerosis, which has a lower concentration of HDL-C as compared to controls [14, 15]. Consequently, the advancement of more dependable indicators of lipid metabolic status is crucial for the formulation of predictive and management approaches in endometriosis. The newly recognized lipoprotein index, representing the ratio of non-HDL cholesterol to HDL cholesterol (NHHR), has emerged as a focal point in recent research. By considering the integrated effects of non-HDL-C and HDL-C, this method provides more extensive lipid metabolism assessment, thereby overcoming the constraints associated with individual lipid indicators [16]. As demonstrated in previous studies [17–19], NHHR has been shown to demonstrate heightened predictive power in evaluating the probability of various diseases, including depression, kidney stones, and cardiovascular-kidney-metabolic syndrome, when contrasted with conventional lipid indicators. Since HDL-C and non-HDL-C levels are known to exhibit sex-specific patterns in the population [20, 21], NHHR may also vary by sex. However, the elucidation of the connection between NHHR and endometriosis is still pending.

Hence, this study sought to employ National Health and Nutrition Examination Survey (NHANES) information spanning from 1999 to 2006 to establish if NHHR is associated with the probability of developing endometriosis. Concurrently, a new research avenue emerged, investigating the predictive potential of NHHR in endometriosis outcomes.

## Methods

### Population

NHANES is a key research initiative conducted by the National Center for Health Statistics (NCHS) that provides a comprehensive overview of the nutritional well-being and overall health of the American population residing outside of institutions. Detailed health information, including demographic, economic situation, nutritional intake, and medical history, was collected at the Mobile Examination Center (MEC), which also involved a suite of physiological assessments and laboratory examinations. Approval for data collection in NHANES was granted by the National Center for Health Statistics' Ethics Review Board, with informed consent secured from all participants prior to the commencement of the survey.

The study utilized four NHANES data releases spanning from 1999 to 2006, which included 41,474 participants. This research employed the following constraints regarding participant inclusion: (1) males ($n = 20{,}264$); (2) individuals under 20 years of age or over 54 years of age ($n = 9{,}120$); (3) lack of data on endometriosis ($n = 6{,}515$); (4) lack of data on the NHHR component ($n = 294$); and (5) lack of covariates ($n = 291$), this included missing information on the marital status ($n = 147$), contraceptive history ($n = 11$), body mass index (BMI, $n = 44$) and age at menarche ($n = 89$). Ultimately, the study comprised 4,636 participants without endometriosis and 354 individuals diagnosed with the condition; refer to Fig. 1.

### Assessment of endometriosis

Endometriosis diagnosis relied upon replies to the Reproductive Health Questionnaire (RHQ360). The responses provided by participants to the question "Has a doctor

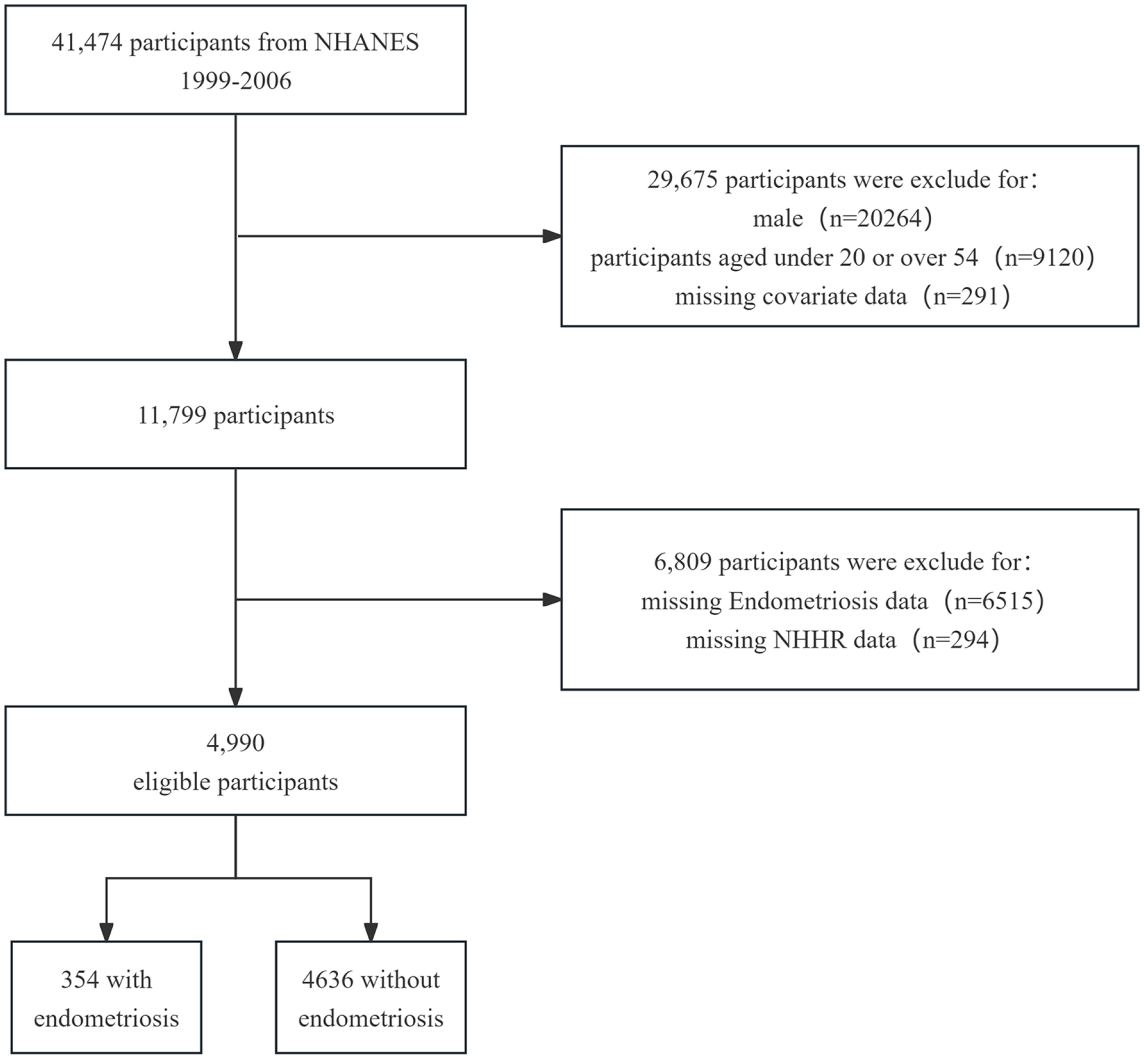


**Fig. 1** Flowchart of eligible participants selection. Flowchart of participant selection from the NHANES 1999–2006 dataset. A total of 41,474 participants were initially considered. After excluding participants based on gender, age, and missing covariate data, 11,799 participants remained. Further exclusions were made for missing endometriosis or NHHR data, resulting in 4,990 eligible participants, with 354 participants diagnosed with endometriosis and 4,636 participants without endometriosis

or other health professional ever told you that you have endometriosis (age 20–54 years at the time of the interview)?", if they answered "Yes", they were assigned to the endometriosis cohort. Conversely, those who answered "No" were classified into the control group. Although there may be a degree of uncertainty associated with relying on question responses to determine the presence or absence of endometriosis, it has been shown that women with endometriosis recall their own diagnostic history with greater than 70% accuracy [22]. Furthermore, several previous NHANES studies have demonstrated the feasibility of using self-reported data to diagnose endometriosis [23, 24].

### Calculation of NHHR

NHHR is derived from an individual's lipid profile and is calculated by first determining the non-HDL-C level, which is the total cholesterol minus HDL-C, and then dividing the non-HDL-C value by the HDL-C value, which follows the methodology described in a previous study [25].

### Inclusion of covariates

Prior research informed the inclusion of demographic, behavioral, and health-related covariates [23, 24]. Sociodemographic details, including age, race, education level, and marital status, were self-reported and collected through the demographic questionnaire. Lifestyle behaviors were assessed based on the questionnaire, incorporating drinking status, with participants

defined as drinkers if they had > 12 drinks in their lifetime and no for the rest; smokers were defined as having ≥ 100 cigarettes in their lifetime. Physical activity levels were assessed using NHANES data, specifically the metabolic equivalent (MET) scores and the weekly duration (in minutes) spent on each activity. A threshold of 450 MET-minutes per week was used to evaluate whether sufficient exercise was achieved. Individuals meeting or exceeding this threshold were classified as sufficiently active, while those falling short were categorized as insufficiently active. Age at first menstruation and oral contraceptive use (yes or no) were obtained from the Reproductive Health Questionnaire RHQ010 ("At what age did the onset of menstruation occur?") and RHQ420 ("Ever taken the pill for any reason?"). Health metrics include measurements such as BMI. A physician has ever diagnosed you with hypertension, and you have used antihypertensive medication or if the average blood pressure exceeds the threshold value of 140/90 mmHg, respectively, meeting any of these criteria would classify you as hypertensive; otherwise, participant would be defined as non-hypertensive. Similarly, diabetes mellitus was identified through a physician's diagnosis. An HbA1c level exceeding the normal range, a fasting blood glucose level above the established threshold, or self-reported diagnosis.

#### Statistical analysis

In this study, continuous variables are expressed as the mean ± standard deviation (SD). To compare these variables between the two groups, a weighted t-test was employed. Categorical variables were described as frequencies and proportions [n (%)]. Group differences were assessed using chi-square ($\chi^2$) tests. NHHR is a continuous variable, and with reference to previous studies [18, 19], we adopted a widely used method of transforming continuous variables in epidemiology into categorical variables [26] by dividing NHHR into four groups through the quartile method in order to further analyze its relationship with endometriosis. Specifically, the quartiles in this study were defined as follows: Q1 (≤ 1.796), Q2 (1.797–2.440), Q3 (2.441–3.250), and Q4 (> 3.250), with Q1 serving as the reference category. In our study, sampling weights were applied to accurately reflect the complex, multistage, stratified, and clustered sampling design of NHANES. Sampling weights were used to ensure that the results of the study were representative of the U.S. civilian noninstitutionalized population and to help minimize potential bias that may result from unequal probabilities of selection and nonresponse. In selecting weights and combining weights, the weights corresponding to the smallest subsample population covering all study variables were used in accordance with guidelines published by the Centers for Disease Control and Prevention (CDC) (https://wwwn.cdc.gov/nchs/nhanes/tutorials/default.aspx). Specifically, the data used in this study included biochemical assays (TC and HDL-C) from MEC, so MEC subsample weights were used. In order to combine the data from the four cycles 1999–2006 and to ensure that the results obtained are statistically nationally representative, we recalculated the sampling weights. For data from the 1999–2002 cycle, we used 1/2 × WTMEC4YR, and for data from the 2003–2006 cycle, we used 1/2 × WTMEC2YR, thus constructing new weights of 1/2 × WTMEC4YR + 1/2 × WTMEC2YR. We employed weighted multivariate logistic regression analysis to examine the predictive power of the NHHR index in relation to endometriosis, which allowed us to estimate odds ratios (OR) and 95% confidence intervals (CI). Model 1 excluded adjustments for covariates. Model 2 was adjusted to account for age, BMI, and HDL levels. Model 3 was adjusted to account for all factors identified through a weighted univariate logistic regression analysis. Based on previous studies [23, 24], which identified these factors as potentially influencing the relationship between NHHR and EMs, including age, race, HDL-C levels, education background, marital status, BMI, smoking and drinking, and a history of hypertension or diabetes. Additionally, age at first menstruation and contraceptive use were considered. To examine the potential nonlinear association between NHHR and risk of endometriosis, restricted cubic spline (RCS) regression was performed. RCS is the fit of a cubic polynomial function to the NHHR with smooth transitions at predefined knots (set at the 5th, 35th, 65th, and 95th percentiles) [27]. RCS regression provides better simplicity and better control of residual confounding than simple linear or categorical models [28]. We used the Wald test to assess overall and nonlinear associations; p was used for overall and for assessing the overall association between the NHHR and EMs, while the nonlinear p-value was used to test for the presence of a significant nonlinear relationship. In addition, we generated scatter plots overlaid with locally estimated scatterplot smoothing (LOESS) curves to provide a more intuitive visualization of the relationship between NHHR and the prevalence of endometriosis. To further investigate, subgroup analyses and interaction tests based on Model 3 were conducted to assess potential variations in the relationship between NHHR and endometriosis across various groups, covering a wide range of possible confounders such as race, age, educational background, marital status, BMI, cardiovascular disease such as hypertension, smoking status, drinking status, and a history of contraceptive use. We also used a likelihood ratio test (LRT) to compare the goodness of fit of models that included interaction terms with those that did not to assess the significance of the interaction. Inferential

results were regarded as significant when $p < 0.05$. The statistical analyses conducted in this study were all executed utilizing R 4.3.1 software.

## Results

### Comparison of demographic characteristics between the endometriosis group and the non-endometriosis group

Table 1 demonstrates the demographic characteristics of the weighted sample. The study included 4,990 participants, which, when weighted, represent a population of 91,008,445 women in the United States. In the weighted sample, participants without a diagnosis of endometriosis had a mean age of 37.29 ± 10.09 years, whereas participants diagnosed with endometriosis had a mean age of 40.96 ± 7.95 years. The study cohort comprised 2,318 non-Hispanic White participants, accounting for 68.91% of the total sample. It is worth noting that women with endometriosis have significantly different characteristics compared to non-affected individuals, especially being more likely to be older, be married, smoking, taking contraceptives, having a higher level of education, and not having high blood pressure ($p < 0.05$). However, there was no significant difference in BMI between the two groups ($p > 0.05$).

### Correlation of NHHR with endometriosis

NHHR was positively associated with the risk of endometriosis, as shown in Table 2. This statistically significant relationship was maintained in Model 1, Model 2 and Model 3. After controlling for all covariates, each 1-unit increase in NHHR was associated with a 17% higher risk of endometriosis (OR = 1.17, 95% CI: 1.05–1.35, $p = 0.04$). To further explore the association, we categorized NHHR into four groups based on quartiles and used Q1 as the reference group. The results showed no significant increase in the risk of endometriosis in groups Q2 and Q3 compared to group Q1, however, group Q4, with the highest NHHR levels exhibited a higher likelihood of endometriosis development in Model 1 (OR = 1.46, 95% CI: 1.03–2.07, $p = 0.04$), and the association remained significant in Model 2 (OR = 1.74, 95% CI: 1.03–2.94, $p = 0.04$). However, in fully adjusted Model 3, although NHHR as a continuous variable was significantly associated with an increased risk of endometriosis, it did not reach statistical significance in the Q4 group compared to Q1 (OR: 1.09,95% CI: 0.87–2.52, $p = 0.15$) and the trend across quartiles was not significant ($p$ for trend = 0.11). The RCS model (see Fig. 2) demonstrated a direct correlation between NHHR and the incidence of endometriosis (non-linear $P = 0.1315$). To further illustrate this relationship, we also visualized the scatterplot of the results by means of a LOESS curve, which showed a trend of increasing prevalence of endometriosis with increasing NHHR (see Fig. 3).

### Subgroup analysis of NHHR and EMs

To determine whether the outcomes of the multivariate regression analyses were influenced by underlying factors, stratified associations between NHHR and endometriosis were examined in more detail, considering a range of factors, including race, age, education level, marital status, BMI, hypertension, smoking status, alcohol consumption, contraceptive use, and age at menarche. Stratified analyses (see Fig. 4) revealed a strong correlation, with NHHR positively impacting EMs in the cohort of individuals who consumed alcohol, while there was no significant effect ($p > 0.05$) on the association in race, age, educational background, marital status, BMI, hypertension, smoking status, history of contraceptive use, and age at menarche, and a significant interaction effect was also observed for alcohol consumption ($p$ for interaction < 0.05).The trend toward increased NHHR versus EMs was consistent across subgroups except for drinking status. Detailed stratification and interaction results are provided in Table S1.

## Discussion

In this study, we included 4,990 participants to examine the link between NHHR and the likelihood of endometriosis within a cohort of the US population. In the continuous variable model, after adjusting for relevant covariates, NHHR showed a positive association with the likelihood of endometriosis. This finding underscores the NHHR's likely clinical relevance in the early identification of endometriosis.

Even lacking prior studies investigating the involvement of NHHR in EMs, documented evidence has been found to suggest a correlation between dyslipidemia and endometriosis. A body of research has demonstrated that patients diagnosed with endometriosis exhibit abnormal lipid levels, including decreased HDL-C concentrations and increased levels of TG, TC, and LDL [29, 30]. Conversely, studies have demonstrated that women diagnosed with endometriosis exhibit higher HDL levels in comparison to those not afflicted with the condition [11, 13]. Moreover, existing studies [31, 32] have shown that there is no significant or consistent association between endometriosis and triglyceride levels, while low-density lipoprotein cholesterol (LDL-C) levels are negatively associated with endometriosis. These traditional lipid markers help assess the risk of EMs, but their findings remain controversial. Consequently, the incorporation of novel lipid parameters may enhance our understanding of the correlation between lipids and the probability of EMs, which requires warrants more comprehensive exploration. In our research, we observed that the continuous NHHR model yielded results that were superior to those of the categorical NHHR models. Despite the direction of the correlation revealed by both of these

**Table 1** Demographic characteristics of the study population

| Characteristic | Overall (*n* = 4990) | Non-endometriosis (*n* = 4636) | Endometriosis (*n* = 354) | *P* value |
|---|---|---|---|---|
| Age(years), mean (SD) | 37.63 (9.97) | 37.29 (10.09) | 40.96 (7.95) | < 0.001*** |
| Age, n(%) | | | | < 0.001*** |
| 20–29 | 1,497.00(22.75%) | 1,455.00 (24.20%) | 42.00 (8.53%) | |
| 30–39 | 1,294.00 (25.51%) | 1,200.00 (25.85%) | 94.00 (22.16%) | |
| 40–49 | 1,206.00 (29.01%) | 1,082.00 (27.59%) | 124.00 (43.01%) | |
| >=50 | 993.00 (22.73%) | 899.00 (22.37%) | 94.00 (26.29%) | |
| Race, n(%) | | | | < 0.001*** |
| Mexican American | 1,195.00 (8.38%) | 1,165.00 (8.97%) | 30.00 (2.59%) | |
| Non – Hispanic White | 2,318.00 (68.91%) | 2,075.00 (67.40%) | 243.00 (83.78%) | |
| Non – Hispanic Black | 1,012.00 (12.00%) | 951.00 (12.39%) | 61.00 (8.19%) | |
| Other Hispanic | 245.00 (5.28%) | 238.00 (5.62%) | 7.00 (1.93%) | |
| Other races | 220.00 (5.41%) | 207.00 (5.61%) | 13.00 (3.51%) | |
| Education, n(%) | | | | < 0.001*** |
| Below high school | 1,188.00 (14.72%) | 1,148.00 (15.25%) | 40.00 (9.51%) | |
| High school | 2,701.00 (62.49%) | 2,479.00 (62.64%) | 222.00 (61.02%) | |
| Above high school | 1,101.00 (22.78%) | 1,009.00 (22.10%) | 92.00 (29.47%) | |
| Marital status, n(%) | | | | < 0.001*** |
| Unmarried | 1,465.00 (27.10%) | 1,404.00 (28.22%) | 61.00 (16.10%) | |
| Married | 3,525.00 (72.90%) | 3,232.00 (71.78%) | 293.00 (83.90%) | |
| BMI (kg/m$^2$), n(%) | | | | 0.625 |
| Normal weight | 1,730.00 (40.52%) | 1,608.00 (40.64%) | 122.00 (39.33%) | |
| Overweight | 1,832.00 (33.79%) | 1,703.00 (33.91%) | 129.00 (32.56%) | |
| Obese | 1,428.00 (25.70%) | 1,325.00 (25.45%) | 103.00 (28.12%) | |
| Physical activity, n(%) | | | | 0.602 |
| Inactive | 1,906.00 (30.40%) | 1,788.00 (30.26%) | 118.00 (31.77%) | |
| Active | 3,084.00 (69.60%) | 2,848.00 (69.74%) | 236.00 (68.23%) | |
| Smoking, n(%) | | | | 0.004** |
| Yes | 1,908.00 (42.65%) | 1,744.00 (41.76%) | 164.00 (51.41%) | |
| No | 3,082.00 (57.35%) | 2,892.00 (58.24%) | 190.00(48.59%) | |
| Alcohol user, n(%) | | | | 0.231 |
| Yes | 220.00 (4.05%) | 207.00 (4.19%) | 13.00 (2.70%) | |
| No | 4,770.00 (95.95%) | 4,429.00 (95.81%) | 341.00 (97.30%) | |
| Hypertension, n(%) | | | | 0.001*** |
| Yes | 1,028.00 (21.82%) | 912.00 (21.05%) | 116.00 (29.37%) | |
| No | 3,962.00 (78.18%) | 3,724.00 (78.95%) | 238.00 (70.63%) | |
| Diabetes, n(%) | | | | |
| Yes | 130.00 (2.26%) | 121.00 (2.27%) | 9.00 (2.14%) | 0.917 |
| No | 4,860.00 (97.74%) | 4,515.00 (97.73%) | 345.00 (97.86%) | |
| Oral contraceptive, n(%) | | | | < 0.001*** |
| Yes | 3,797.00 (80.52%) | 3,478.00 (79.42%) | 319.00 (91.37%) | |
| No | 1,193.00 (19.48%) | 1,158.00 (20.58%) | 35.00 (8.63%) | |
| Menarche Age, mean(SD) | 12.59 (1.68) | 12.62 (1.68) | 12.37 (1.70) | 0.068 |
| HDL(mg/dl) | 58.02 (16.08) | 58.03 (16.01) | 57.96 (16.70) | 0.826 |
| TC(mg/dl) | 196.78 (40.22) | 195.92 (39.94) | 205.18 (42.05) | 0.002** |
| NHHR | 2.63 (1.25) | 2.61 (1.22) | 2.85 (1.52) | 0.045* |
| NHHR Quantile, n(%) | | | | 0.069 |
| Q1 (≤ 1.796) | 1,173.00(25.16%) | 1,093.00(25.40%) | 80.00(22.80%) | |
| Q2(1.797–2.440) | 1,235.00(24.92%) | 1,151.00(25.29%) | 84.00(21.29%) | |
| Q3(2.441–3.250) | 1,314.00(24.94%) | 1,232.00(25.03%) | 82.00(24.07%) | |
| Q4(> 3.250) | 1,268.00(24.98%) | 1,160.00(24.28%) | 108.00(31.84%) | |

Note: BMI: body mass index; HDL: high density lipoprotein cholesterol; TC: total cholesterol; *$P$<0.05, ** $P$<0.01,*** $P$<0.001

**Table 2** Association of the NHHR with endometriosis

| Exposure | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | *p* -value | OR (95% CI) | *p* -value | OR (95% CI) | *p* -value |
| NHHR | 1.15(1.04,1.27) | 0.01** | 1.21(1.04,1.42) | 0.02* | 1.17(1.05,1.35) | 0.04* |
| NHHR Quartile | | | | | | |
| Q1(≤ 1.796) | Reference | | Reference | | Reference | |
| Q2(1.797–2.440) | 0.94(0.65,1.35) | 0.72 | 1.02(0.69,1.52) | 0.91 | 0.98(0.67,1.46) | 0.93 |
| Q3(2.441–3.250) | 1.07(0.79,1.45) | 0.66 | 1.24(0.83,1.84) | 0.30 | 0.92(0.76,1.66) | 0.57 |
| Q4(> 3.250) | 1.46(1.03,2.07) | 0.04* | 1.74(1.03,2.94) | 0.04* | 1.09(0.87,2.52) | 0.15 |
| P for trend | | 0.02* | | 0.04* | | 0.11 |

Note: 95% CI:95% confidence interval; OR: odds ratio.*$P<0.05$, ** $P<0.01$

Model 1: unadjusted model

Model 2: adjusted for Age, BMI, HDL

Model 3: further adjusted for education, marital status, smoking, drinker, hypertension, race, diabetes, age at menarche, and the use of contraceptive pills

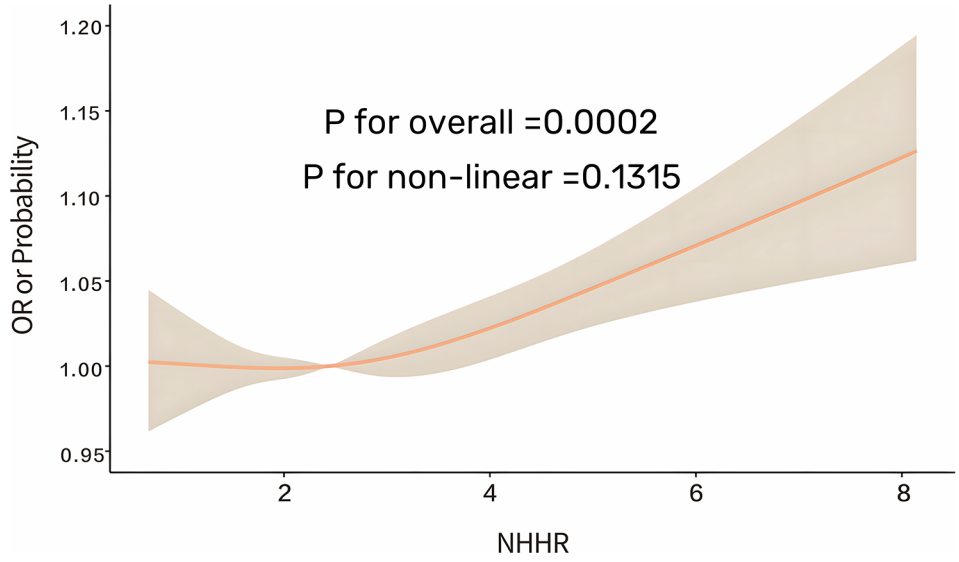


**Fig. 2** Restricted cubic splines for associations between NHHR and endometriosis. "Odds Ratio" represents the solid line, showing the trend of OR or probability as NHHR values change."Confidence Interval" represents the shaded area, showing the confidence interval range for OR or probability

models being positive, it should be interpreted with caution. NHHR represents a novel composite lipid indicator that, unlike traditional lipid markers, represents the equilibrium existing between HDL-C and non-HDL-C, thereby offering a more thorough evaluation of their lipid health status. An increase in NHHR could suggest a disruption in the metabolism of lipids [33]. The relationship observed in this study, high NHHR is associated with the occurrence of EMs, suggesting that disrupted lipid balance potentially contributes to the EMs phenotype. However, the particular physiological pathways linking NHHR to endometriosis are still not fully elucidated, and several possible pathways are suggested as underlying mechanisms in current research, including inflammatory responses and oxidative stress, altered hormone levels, and immune modulation.

First, NHHR may promote endometriosis formation by modulating inflammation and oxidative stress. There is evidence that women with EMs exhibit elevated concentrations of cytokines, such as IL-1β, IL-8, TNF-α, among others [34]. These cytokines have been shown to intensify the localized inflammatory reaction in endometriotic lesions, thereby influencing the onset and progression of the disease [35]. Increased concentrations of non-HDL-C components may exacerbate endometriosis by activating monocytes and macrophages to release pro-inflammatory factors [36–39]. Secondly, oxidation products of non-HDL-C, such as oxidized LDL (Ox-LDL), may contribute to endometriosis by inducing oxidative stress and subsequently releasing pro-inflammatory factors, thereby increasing the likelihood of disease progression and persistence [40]. It has been demonstrated that individuals with EMs exhibit significantly elevated levels of ox-LDL within their peritoneal fluid environment [41]. Moreover, reduced HDL-C levels diminish the body's capacity to counteract inflammatory processes, exhibit antioxidant properties and provide endothelial support, potentially increasing the risk of developing

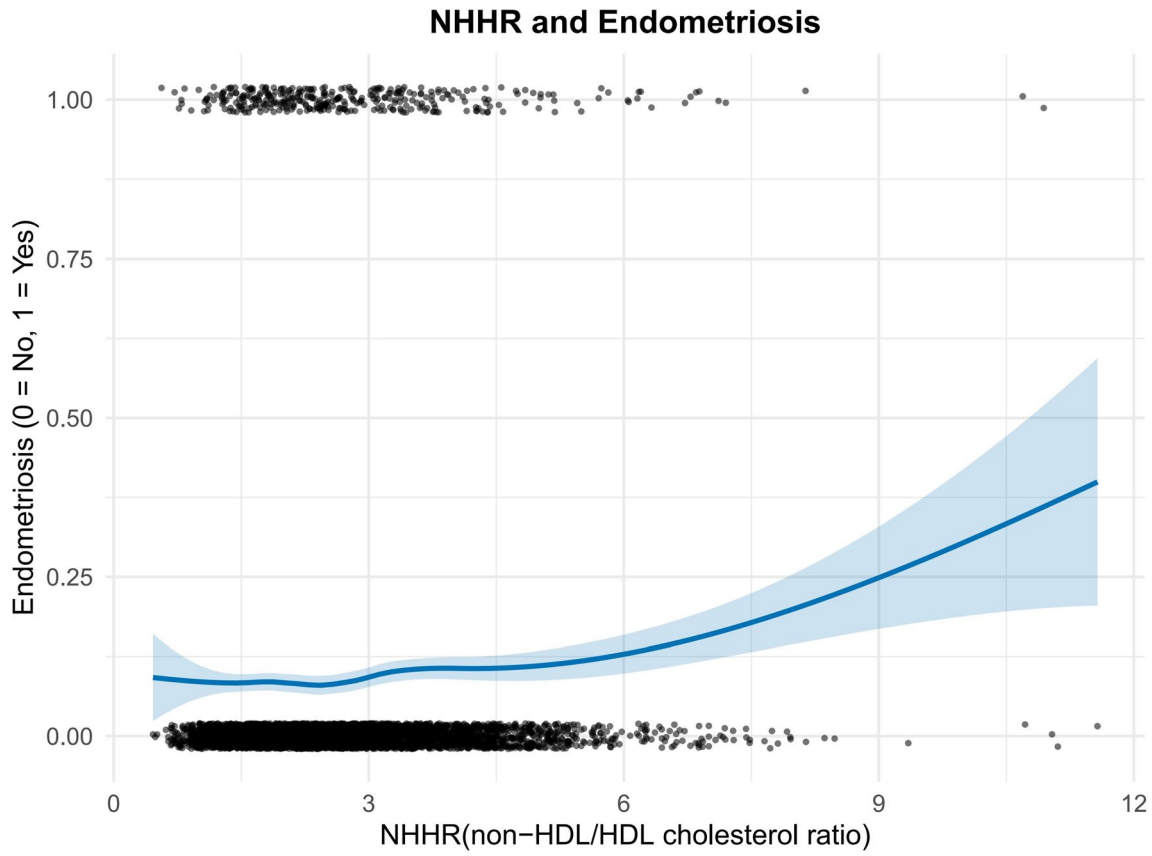


**Fig. 3** Scatterplot of the association between NHHR and the prevalence of endometriosis with LOESS smoothing. The solid line represents the LOESS-smoothed trend, and the blue shaded area indicates the 95% confidence interval. Each point represents an individual observation. The LOESS curve illustrates an overall increasing trend in endometriosis prevalence with rising NHHR

endometriosis [42, 43]. In contrast, within the chronic inflammatory environment of endometriosis, HDL particles may carry pro-oxidant substances such as oxidized phospholipids, which activate peritoneal macrophages and mesothelial cells, leading to the release of chemokines and perpetuating the chronic inflammatory cycle [44, 45]. In addition, NHHR could potentially impact the pathophysiological mechanisms underlying endometriosis through modulating the function of immune cells that are pivotal in the onset and advancement of this condition [36, 46–48]. Specifically, higher values of NHHR are indicative of relatively lower concentrations of HDL-C, leading to diminished functionality to demonstrate anti-inflammatory properties and could alter the body's immune status, further weakening immune surveillance and potentially contributing to disease progression [46, 49, 50]. Beyond these mechanisms, body mass index (BMI) is also a potential factor thought to influence the development and progression of endometriosis through mechanisms such as chronic inflammation, estrogen metabolism, and abnormal secretion of adipokines (e.g., leptin). Although BMI may influence certain physiological mechanisms, no significant differences were found between the case and control groups in this study, and the interaction between BMI and NHHR was not statistically significant. This finding aligns with some studies [51], suggesting BMI plays a minor role in NHHR-related pathogenic pathways or is limited by the study's sample distribution and statistical power. Given the complex relationship between BMI and endometriosis, along with the ongoing controversy surrounding these factors [52, 53], further research is warranted.

Furthermore, NHHR may also influence the pathogenesis of endometriosis by modulating estrogen synthesis. When NHHR increases, it indicates an elevation in non-HDL-C or a reduction in HDL-C. On one hand, an elevation in non-HDL-C levels can provide abundant cholesterol substrates for estrogen biosynthesis [54]. Studies [55] have shown that key enzymes in cholesterol metabolism (such as StAR protein and aromatase) exhibit upregulated expression in ectopic endometrial tissue. These enzymes can mediate the local conversion of cholesterol to estrogen, leading to significantly higher estrogen concentrations within the lesions compared with normal tissues thereby forming an autocrine/paracrine loop. On the other hand, a decrease in HDL-C

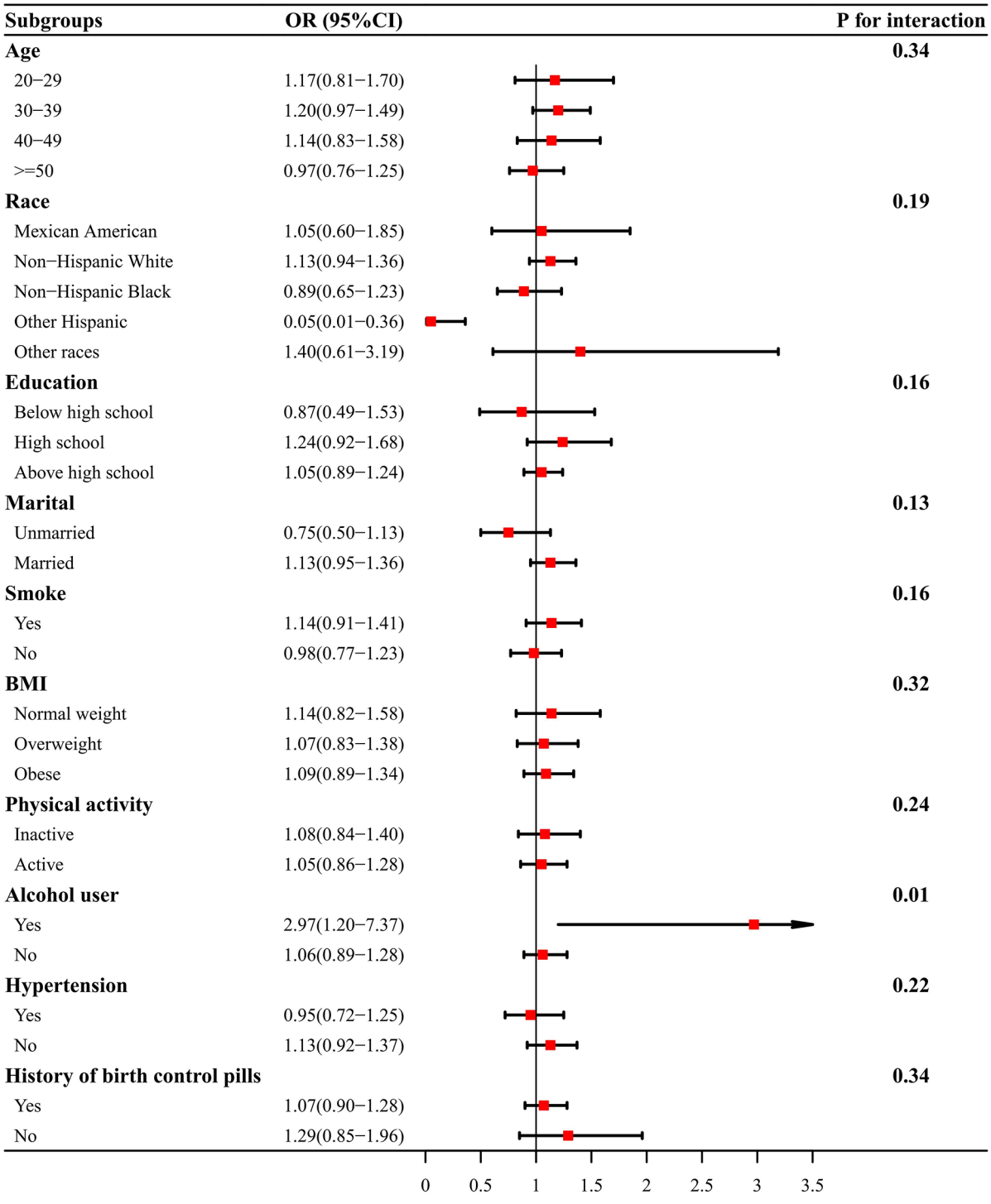


**Fig. 4** Subgroup analysis of the association between NHHR and endometriosis. The OR and 95% CI for each subgroup are shown, along with p-values for interaction. Subgroups include age, race, education, marital status, smoking status, BMI, physical activity, alcohol use, hypertension, and history of birth control pills. Significant findings are indicated by the red squares

levels impairs reverse cholesterol transport, leading to cholesterol accumulation and thereby providing more substrates for local estrogen production [43]. Notably, excessive estrogen stimulation plays a key role in endometriosis development by promoting ectopic endometrial cell survival and proliferation through multiple pathways and upregulating vascular endothelial growth factor (VEGF) expression to enhance angiogenesis [56]. To summarize, in order to gain a thorough insight into this

correlation, future investigations need to explore the precise fundamental mechanisms.

Meanwhile, subgroup stratification analysis in the present study demonstrated a stronger positive link between NHHR and the occurrence of endometriosis among the drinking population. This result aligns partially with previous studies, which indicate that alcohol potentially influences the risk of endometriosis through multiple pathways. Studies have demonstrated that excessive alcohol intake inhibits hepatic lipoprotein metabolism, resulting in higher concentrations of non-HDL-C and a impaired antioxidant capacity of HDL-C [57, 58], thereby exacerbating lipid peroxidation and inflammatory responses. In addition, the alcohol metabolite acetaldehyde influences pro-inflammatory pathways and oxidative stress [59, 60], thereby potentially increasing the risk of endometriosis. It is worth noting that recent studies [61] in the general population have revealed that compared with those who never drink, individuals who start drinking exhibit lower non-HDL (such as LDL) and higher HDL levels, while those who previously drank but quit show increased non-HDL and decreased HDL. In women without endometriosis, moderate alcohol consumption may temporarily raise HDL-C levels [62], but long-term drinking, especially around menopause, can disrupt lipoprotein structure, leading to decreased HDL-C and a potential increase in NHHR [57]. The combined effect of acute metabolic improvement and chronic pathological damage may help explain the strengthened association between NHHR and endometriosis observed among drinkers in this study. Consequently, associating NHHR with the probability of endometriosis development might be more significant among populations that consume alcohol.

NHHR represents a unique biomarker for lipid metabolism, exhibiting significant clinical importance in the early detection and therapy of endometriosis. In our research, a noteworthy correlation was observed between NHHR and the likelihood of endometriosis, especially among alcohol consumers. In clinical practice, women with elevated NHHR levels who consume alcohol could be screened more intensively and advised to mitigate their risk of disease progression through lifestyle interventions, such as alcohol restriction and adopting low-fat diets rich in omega-3 fatty acids and Mediterranean-style dietary patterns [63]. This proactive screening strategy may not only reduce reliance on invasive diagnostic procedures such as laparoscopy but also provide patients with a more timely treatment window. Notably, the dynamics of NHHR provide a critical foundation for the individualized treatment of EMs. For patients with elevated NHHR levels, the likelihood of developing endometriosis is increased as well. Therefore, estrogen levels can be reduced using gonadotropin-releasing hormone (GnRH) agonists or aromatase inhibitors to suppress the activity of ectopic lesions [64, 65]. Alternatively, statins such as atorvastatin may help improve lipid profiles and attenuate oxidative stress and the inflammatory microenvironment [66]. Additionally, a higher NHHR may reflect an underlying risk of cardiometabolic conditions such as heart disease, diabetes, and stroke, as supported by prior epidemiological evidence [67, 68].Given the systemic inflammatory and metabolic nature of endometriosis, elevated NHHR may also indicate a shared pathophysiological mechanism. Thus, NHHR could serve as a potential biomarker not only for screening endometriosis but also for identifying patients at higher risk of cardiometabolic comorbidities, highlighting the need for early prevention strategies. The introduction of NHHR offers a novel perspective on the early screening and management of EMs with its advantages in affordability, accessibility, and dynamic monitoring addressing clinical requirements.

## Advantages and limitations

This study has several key strengths. First, leveraging data from the nationally representative NHANES dataset with rigorous sampling weights ensures our findings are generalizable to the U.S. population, enhancing external validity. Second, we used weighted logistic regression and RCS modeling along with LOESS visualization to explore NHHR and endometriosis associations. This dual approach allowed flexible exploration of associations, while subgroup analyses confirmed consistent findings across different populations. Third, we adjusted for a wide range of potential confounders and conducted subgroup analyses to examine the consistency of the results. Lastly, by introducing NHHR as a combined lipid metric, this study fills a research gap in endometriosis-lipid links, aiding future risk studies. Nevertheless, this study has several limitations. First, due to its cross-sectional design, causal relationships between NHHR and endometriosis cannot be established. Second, the diagnosis of endometriosis relied on self-reported data, which may be subject to recall bias. However, recent studies [22] suggest that women with endometriosis may recall their diagnostic history with reasonable accuracy, which may help mitigate this bias to some extent. In addition, the NHANES database lacks clinical confirmation, which may further affect diagnostic validity. Future studies incorporating clinical diagnostic records may help improve accuracy and reduce potential bias. Third, although we adjusted for multiple known and suspected confounders, residual confounding from unmeasured variables (e.g., parity, hormone levels, surgical history, and other gynecological conditions) cannot be ruled out. More comprehensive covariate control may improve the validity of future analyses. Additionally, different stages of endometriosis,

as defined by the Revised American Society for Reproductive Medicine (rASRM), may show distinct biological and clinical features, which could affect its association with NHHR. Future studies should validate these findings in broader populations and incorporate stage-based stratified analyses to draw more robust and generalizable conclusions. Lastly, the use of NHANES 1999–2006 data may limit temporal applicability, which may benefit from validation using more recent or longitudinal datasets.

## Conclusion

Overall, this research establishes a link between NHHR and increased risk of endometriosis in the US population. To more comprehensively validate the findings of this study, future research could explore diverse experimental designs. In addition, further studies can help to elucidate the underlying mechanisms.

**Abbreviations**

| | |
|---|---|
| BMI | Body Mass Index |
| CI | Confidence Interval |
| CDC | Centers for Disease Control and Prevention |
| EMs | Endometriosis |
| GnRH | Gonadotropin-Releasing Hormone Agonists |
| HDL-C | High-Density Lipoprotein Cholesterol |
| LDL-C | Low-Density Lipoprotein Cholesterol |
| LOESS | Locally estimated scatterplot smoothing |
| LRT | Likelihood ratio test |
| MEC | Mobile Examination Center |
| MET | Metabolic Equivalent |
| NHHR | Non-HDL/HDL Cholesterol Ratio |
| NCHS | National Center for Health Statistics |
| non-HDL-C | Non-High-Density Lipoprotein Cholesterol |
| OR | Odds Ratio |
| Ox-LDL | Oxidized Low-Density Lipoprotein |
| RCS | Restricted Cubic Spline |
| rASRM | Revised American Society for Reproductive Medicine classification |
| SD | Standard Deviation |
| StAR | Steroidogenic Acute Regulatory |
| TG | Triglycerides |
| VEGF | Vascular Endothelial Growth Factor |
| $X^2$ | Chi-square |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02590-x.

Supplementary Material 1

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**Author contributions**
PJ and XZ: Conceptualization, Data analysis, Writing– original draft. HH, ZS and WH: Data curation, manuscript revision. YL*: Supervision, Writing–review & editing.

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**Data availability**
The data used in this study can be accessed through the official website of theNational Health and Nutrition Examination Survey (NHANES). Relevant datasets are available at the following link: https://www.cdc.gov/nchs/nhanes/index.htm.

## Declarations

**Ethics approval and consent to participate**
Approval for data collection in NHANES was granted by the National Center for Health Statistics' Ethics Review Board, with informed consent secured from all participants prior to the commencement of the survey.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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