

The Positive Association Between RCII and Endometriosis and Its Integration into a Clinical Predictive Model: A Cross-Sectional Study

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Introduction: Studies indicate that endometriosis (EMs) is associated with inflammation and metabolic abnormalities. The Remnant Cholesterol Inflammatory Index (RCII) concurrently reflects both inflammatory and metabolic status. However, the relationship between RCII and EMs remains unclear. Therefore, this study aims to investigate the association between RCII and EMs and explore the potential of RCII as a risk predictor for EMs.

Methods: Making use of information from the 1999–2006 NHANES database, we investigated the connection between natural logarithm-transformed RCII (lnRCII) and EMs employing logistic regression analysis, restricted cubic spline (RCS) models, and subgroup analysis approaches. Finally, a nomogram was constructed based on feature variables selected via LASSO regression to enhance the interpretability of the predictive model.

Results: After adjusting for potential confounding factors, lnRCII demonstrated a substantial positive correlation with the risk of EMs. For each 1-standard-deviation increase in lnRCII, the EMs' risk increased by 25% (fully adjusted model OR = 1.250, 95% CI: 1.266–1.461, P = 0.006). Furthermore, a linear relationship between lnRCII and EMS was observed via RCS analysis. According to subgroup analysis, the relationship between lnRCII and EMS has a consistent association across the majority of the population. (P for interaction > 0.05).

Conclusion: In the US population, RCII was substantially linked to a higher risk of EMs, suggesting that the lipid metabolism-inflammation axis may represent a potential target for intervention in the prevention or treatment of EMs.

Keywords: remnant cholesterol inflammatory index, endometriosis, cross-sectional study, NHANES

Introduction

Endometriosis(EMs) is a chronic condition that severely impacts female reproductive health, pathologically characterized by ectopic development of endometrial cells outside the uterus.¹ Endometrium-like tissues may proliferate in extrauterine sites such as ovaries, fallopian tubes, and other pelvic structures, forming cysts or scar tissue.² This pathological process can further trigger complications, including ovarian cancer.^{3,4} Research shows that 190 million women of childbearing age are affected by EMs, which have a prevalence of 5% to 10%.⁵ Among affected women, 50–70% experience pelvic pain and 30–50% develop infertility.⁶ This severely impacts quality of life and mental health, posing a substantial burden on global health.^{7,8} Direct laparoscopic sight of lesions, followed by histological confirmation, is still the gold standard for diagnosing endometriosis.⁹ However, as this

is an invasive procedure, most patients do not receive a diagnosis until around 7 to 8 years after the onset of symptoms, which may result in infertility and the advancement of the condition.¹⁰ Therefore, identifying its associated risk factors and investigating easily accessible biomarkers are crucial for the early diagnosis and treatment of EMs.

In recent years, the relationship between lipid metabolism and inflammation in various diseases has garnered widespread attention. Studies indicate that remnant cholesterol is closely associated with atherosclerosis, inflammatory status, and the risk of systemic diseases.^{11,12} In EMs research, cholesterol and its related biomarkers are considered potentially significant in the onset and progression of this disease.^{13,14} Existing research has demonstrated that elevated remnant cholesterol (RC) levels may be associated with the development and progression of endometriosis.¹⁵ Furthermore, inflammatory indicators such as high-sensitivity C-reactive protein (hs-CRP) and neutrophil-to-lymphocyte ratio have increasingly revealed clinical relevance in endometriosis studies.^{16,17} This may be related to the promotion of lesion proliferation, invasion, and neurovascular network formation through the induction of vascular endothelial growth factor (VEGF) expression in ectopic endometrium by cholesterol metabolism and inflammation, as angiogenesis is a fundamental mechanism for the growth and maintenance of endometrioma lesions.^{18–20}

Although previous research has looked into the relationship between cholesterol metabolism, inflammatory indicators and EMs, the Residual Cholesterol Inflammation Index (RCII) as a predictive risk factor for endometriosis remains unexplored. The RCII has been demonstrated to be associated with metabolic syndrome, the occurrence of cardiovascular diseases, and related mortality.^{21,22} RCII is not a simple composite index; its design is based on a clear pathophysiological mechanism through which RC promotes inflammation. This mechanism includes phagocytosis by macrophages to form foam cells, activation of inflammasomes (such as NLRP3), and increased oxidative stress leading to an inflammatory state.^{23,24} Systemic inflammation, in turn, results in elevated inflammatory markers (such as C-reactive protein). Therefore, RCII is designed to reflect the synergistic or amplifying effect between lipid abnormalities and systemic inflammatory response, offering greater integrative and pathophysiological significance than using RC or CRP alone. EMs is widely recognized as a chronic inflammatory disease, characterized by extensive infiltration of inflammatory cells and high expression of pro-inflammatory factors (such as TNF- α , IL-1 β , IL-6) in the peritoneal microenvironment and local lesions.²⁵ RC contributes to inflammation by increasing oxidized lipid products and may also influence estrogen metabolism, which plays a key role in EMs.²⁶ Consequently, we propose that the RCII metric is well-suited to capture this coexisting state of high lipids and high inflammation, potentially serving as an effective biomarker for identifying the risk or severity of EMs. Evaluating the relationship between RCII and EMs will provide novel insights for early diagnosis and intervention of this disease. Therefore, the purpose of this study is to look at the relationship between the RCII and the risk of EMs.

Methods

Study Population

The National Health and Nutrition Examination Survey (NHANES) database was used in the analysis of this study. Since 1999, NHANES has routinely gathered nutritional and health information from Americans, encompassing demographics, anthropometric measurements, laboratory indicators, dietary habits, and health status. The database features substantial volume and high authenticity. NHANES collects data using a stratified, multistage probability sampling technique to guarantee national representativeness. We included women aged 20 to 54 years from the 1999–2006 cycles who were diagnosed with EMs through self-report or ICD codes, and who had complete lipid profile and inflammatory marker data. By excluding participants with incomplete data, we ensured the accuracy and representativeness of the study population. Ultimately, 2,316 qualified subjects were included, comprising 2,145 in the non-EMs group and 171 in the EMs group. The inclusion process is illustrated in [Figure 1](#). Following the NHANES study protocol, which was authorized by the National Center for Health Statistics' (NCHS) Research Ethics Review Board, each participant gave written informed consent.

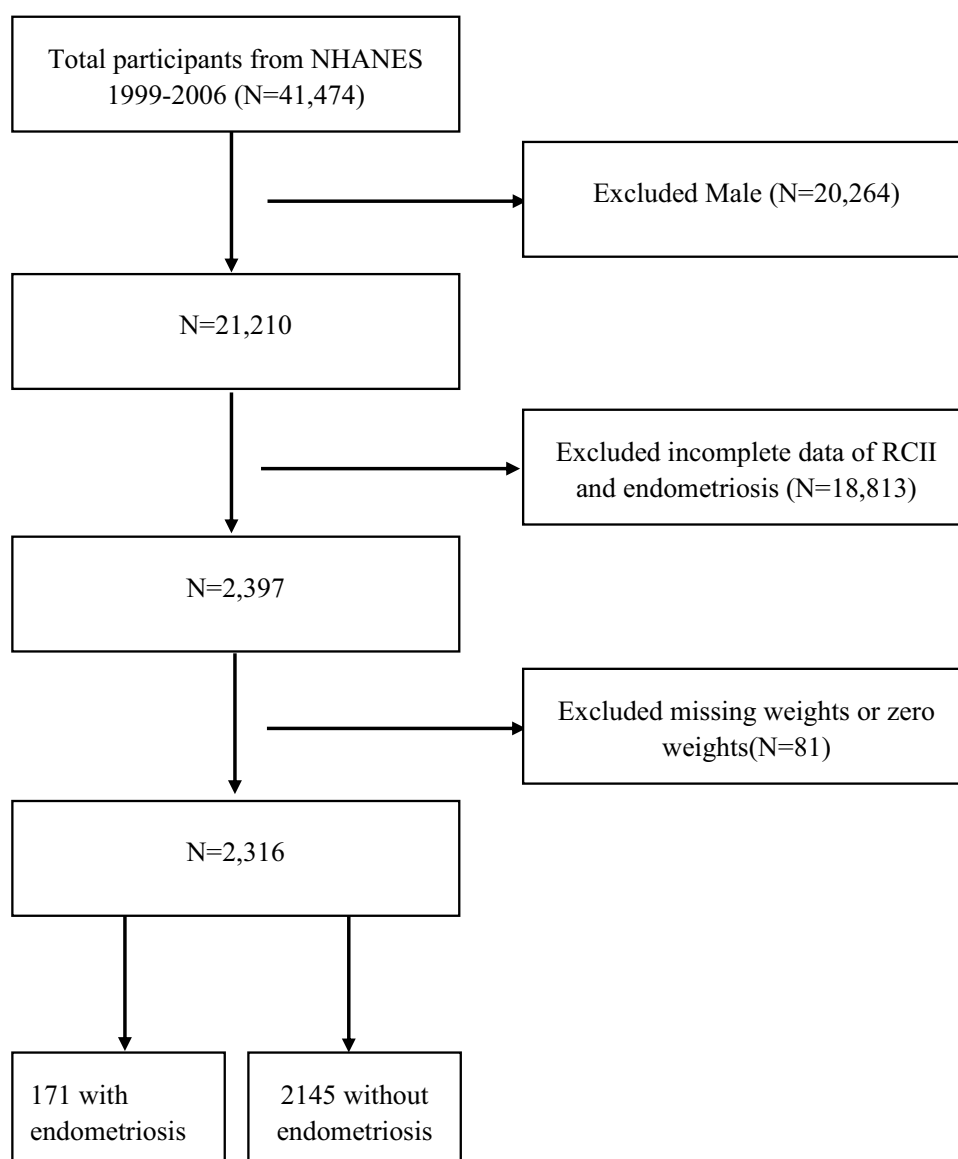


Figure 1 A flowchart illustrating the screening process for selecting endometriosis participants.

Exposure and Outcome Variables

The variable related to exposure in this investigation was the RCII, calculated using the formula: $RCII = [TC - (HDL-C + LDL-C)] \text{ (mg/dL)} \times \text{hsCRP (mg/L)} / 10$.²⁷ Because of the skewed distribution of RCII, a natural logarithmic transformation was applied to obtain $\ln RCII$ (Figure 2). All subsequent statistical analyses were based on this transformed variable. All hematological and biochemical parameters in RCII were measured in participants after a fasting period of at least 9 hours. Enzymatic assays were used to directly measure serum total cholesterol and triglycerides, whereas serum HDL-C was measured via direct immunoassays or enzymatic assays following serum depletion of apolipoprotein B-containing lipoproteins using heparin-Mn²⁺ precipitation. LDL-C was estimated using the Friedewald equation: $LDL-C = TC - HDL-C - TG/5$ (mg/dL). C-reactive protein was measured by a latex-enhanced solution method. Detailed specimen collection and processing instructions are described in the NHANES Laboratory/Medical Technologists Procedures Manual (LPM). The outcome variable in this study was endometriosis (EMs). Data were obtained through questionnaires, where participants answering “YES” to “Told by doctor had endometriosis?” were classified as having EMs.²⁸

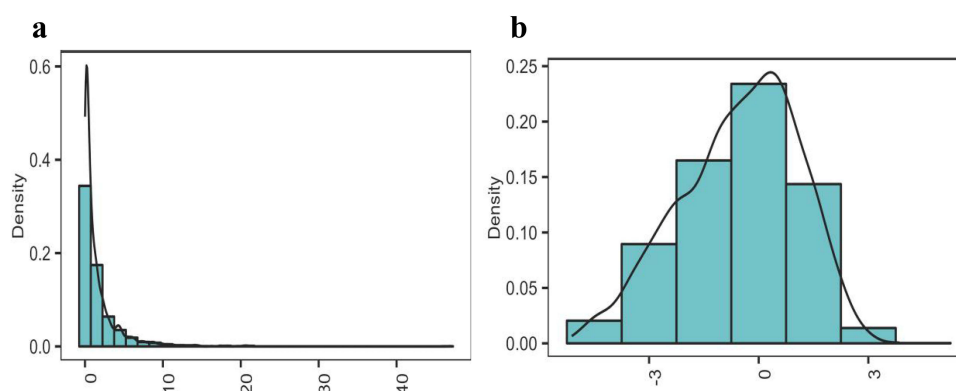


Figure 2 Distribution of RCII before ((a)RCII) and after ((b)lnRCII) natural log transformation.

Covariates

Beyond laboratory indicators related to RCII, we collected additional covariates including: demographic information (age, race, educational background, status in marriage, household income), smoking status, alcohol consumption, body mass index (BMI), triglycerides, fasting blood glucose (FBG), insulin, glycated hemoglobin, age at menarche, menstrual regularity, and clinical chronic diseases (diabetes, hypertension, dyslipidemia). Data on comorbidity were collected through self-reported surveys. Three groups were identified based on smoking status: never smokers (less than 100 cigarettes), past smokers (those who had smoked more than 100 cigarettes but do not smoke now), and current smokers (those who have smoked more than 100 cigarettes and smoke regularly or sometimes). Alcohol intake was defined as consuming 12 or more drinks during one's lifetime, with relevant data obtainable from the file labelled "ALQ".

Statistical Methods

In this research, we grouped participants according to their status of endometriosis diagnosis. For continuous variables, weighted Student's *t*-tests were employed, and for the data with categories, we used weighted chi-square tests. Categorical variables are displayed as proportions, while continuous variables are expressed as mean and standard deviation. We investigated the association between the natural logarithm-transformed RCII (lnRCII) and EMS using weighted logistic regression analysis and multivariate modelling. Three logistic regression models were constructed with progressive adjustments for different confounding factors: Model 1 adjusted for no confounding factors; Model 2 adjusted for age, race, education level, marital status, and income level; Model 3 adjusted for all variables except C-reactive protein, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. We employed restricted cubic spline (RCS) models to visualize the dose-response connection between lnRCII and EMS. Subgroup analysis was conducted to assess the robustness of the relationship between lnRCII and EMs. Furthermore, the Least Absolute Shrinkage and Selection Operator (LASSO) regression model was employed to screen 15 feature variables. Finally, a nomogram was constructed based on the selected 15 variables to enhance the interpretability of the predictive model outcomes.

All statistical analyses were conducted using the DecisionLinnc1.0 software—an intelligent platform supporting multilingual scripting (eg, Python, R, Java, C++) with cloud computing capabilities.²⁹ Its core functionalities encompass data processing, analytical operations, and visualization. Following the Centers for Disease Control and Prevention's recommendations and considering the complex, multistage, clustered design of NHANES, all statistical analyses employed fasting subsample weights to ensure national representativeness.

Results

Baseline Characteristics

Table 1 presents the demographic characteristics and health information of the study participants. This study included 2,316 participants, comprising 171 EMs patients and 2,145 non-EMs individuals. The results indicated that the

Table 1 Baseline Characteristics of Women Participants from the NHANES 1999–2006, Weighted

Characteristic	Overall N = 2,316	Without Endometriosis N = 2,145	With Endometriosis N = 171	p-value
Age (year), mean $\pm$ SE	37.57 $\pm$ 9.88	37.25 $\pm$ 10.01	40.51 $\pm$ 7.97	<0.001
Race (n, %)				<0.001
Mexican American	188 (8.10%)	190 (8.84%)	2 (1.39%)	
Other Hispanic	109(4.71%)	108 (5.03%)	3(1.85%)	
Non-Hispanic white	1,597 (68.97%)	1,447 (67.44%)	142(82.76%)	
Non-Hispanic black	288 (12.42%)	271 (12.66%)	18 (10.27%)	
Other race	134 (5.80%)	129(6.03%)	6 (3.72%)	
Education (n, %)				0.034
Below high school	360 (15.55%)	346 (16.13%)	17 (10.30%)	
High school	520 (22.44%)	465 (21.70%)	50 (29.10%)	
Above high school	1,436 (62.01%)	1,334 (62.17%)	104(60.60%)	
Marital status (n, %)				0.156
Single	793 (34.26%)	752 (35.05%)	46 (27.12%)	
Married or with partner	1,523(65.74%)	1,393 (64.95%)	125 (72.88%)	
Family PIR, mean $\pm$ SE	3.03 $\pm$ 1.58	3.01 $\pm$ 1.57	3.17 $\pm$ 1.65	0.272
BMI, mean $\pm$ SE	28.25 $\pm$ 7.28	28.24 $\pm$ 7.36	28.33 $\pm$ 6.55	0.455
Total cholesterol, mean $\pm$ SE	194.67 $\pm$ 38.62	193.90 $\pm$ 38.50	201.64 $\pm$ 39.15	0.033
Triglyceride, mean $\pm$ SE	115.45 $\pm$ 63.36	113.65 $\pm$ 61.81	131.74 $\pm$ 74.17	0.009
LDL-C, mean $\pm$ SE	113.64 $\pm$ 34.05	113.14 $\pm$ 33.94	118.09 $\pm$ 34.81	0.051
HDL-C, mean $\pm$ SE	57.94 $\pm$ 15.95	58.02 $\pm$ 15.92	57.22 $\pm$ 16.20	0.629
FBG, mean $\pm$ SE	94.56 $\pm$ 20.52	94.72 $\pm$ 21.28	93.10 $\pm$ 11.44	0.938
Insulin, mean $\pm$ SE	10.07 $\pm$ 8.00	10.17 $\pm$ 8.16	9.19 $\pm$ 6.30	0.411
HbA1c, mean $\pm$ SE	5.27 $\pm$ 0.72	5.27 $\pm$ 0.74	5.28 $\pm$ 0.56	0.486
CRP, mean $\pm$ SE	0.51 $\pm$ 0.83	0.51 $\pm$ 0.85	0.53 $\pm$ 0.62	<0.001
Age of menarche, mean $\pm$ SE	12.64 $\pm$ 1.69	12.67 $\pm$ 1.69	12.41 $\pm$ 1.71	0.135
Menstrual regularity (n, %)				<0.001
No	711 (30.71%)	604 (28.14%)	92(53.95%)	
Yes	1,605 (69.29%)	1,541 (71.86%)	79 (46.05%)	
Diabetes (n, %)				0.477
No	2,228 (96.19%)	2,060 (96.06%)	167(97.37%)	
Yes	88 (3.81%)	85 (3.94%)	4 (2.63%)	
Hypertension (n, %)				0.330
No	1,887 (81.46%)	1,754 (81.76%)	135 (78.68%)	
Yes	429(18.54%)	391(18.24%)	36 (21.32%)	
Hyperlipidemia (n, %)				0.008
No	1,863 (80.44%)	1,751 (81.61%)	120 (69.93%)	
Yes	453 (19.56%)	394 (18.39%)	51 (30.07%)	
Smoke (n, %)				<0.001
Never	1,343(57.97%)	1,282 (59.76%)	71 (41.81%)	
Former	401 (17.31%)	361(16.85%)	37(21.50%)	
Now	572(24.71%)	502 (23.39%)	63 (36.69%)	
Alcohol user (n, %)				0.134
No	330(14.27%)	318 (14.84%)	15(9.05%)	
Yes	1,986 (85.73%)	1,827 (85.16%)	156 (90.95%)	
RCII, mean $\pm$ SE	1.38 $\pm$ 2.65	1.35 $\pm$ 2.70	1.60 $\pm$ 2.13	<0.001
lnRCII, mean $\pm$ SE	-0.81 $\pm$ 1.64	-0.85 $\pm$ 1.65	-0.38 $\pm$ 1.48	<0.001

Note: Data are presented as mean (SD) or n (%).

Abbreviations: CI, confidence interval; EMs, endometriosis; PIR, Income to poverty ratio; BMI, body mass index; HbA1c, glycosylated hemoglobin; FBG, fasting blood-glucose; HDL-C, high-density cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; RCII, Remnant Cholesterol Inflammatory Index.

Table 2 Weighted Logistic Regression Analysis of InRCII and EMs

	Model 1 OR, 95% CI, P value	Model 2 OR, 95% CI, P value	Model 3 OR, 95% CI, P value
InRCII	1.200(1.090,1.321) 0.001	1.203(1.088,1.330) 0.001	1.250(1.070,1.461) 0.006
T1	Reference	Reference	Reference
T2	1.590(0.994,2.542) 0.053	1.600(0.983,2.603) 0.058	1.664(0.972,2.847) 0.063
T3	1.984(1.363,2.889) 0.001	1.963(1.324,2.912) 0.001	2.206(1.266,3.845) 0.007
P for trend	1.405(1.174,1.682) 0.001	1.397(1.156,1.689) 0.001	1.485(1.128,1.956) 0.006

Notes: Model 1 was not modified. Model 2 was modified for age, race, education level, marital status and family income level; Model 3 was modified to account for age, race, education level, marital status, family income level, BMI, fasting glucose, HbA1c, insulin, triglycerides, smoking status, alcohol consumption, hypertension, diabetes, hyperlipidemia, age at menarche, and menstrual regularity.

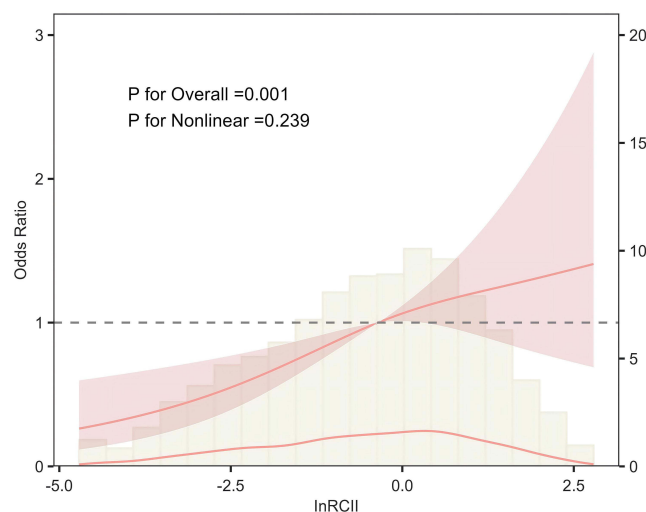
differences between the EMs and non-EMs were statistically significant ($p < 0.05$) regarding age, race, education level, cholesterol, triglycerides, C-reactive protein, menstrual regularity, hyperlipidemia, smoking status, and InRCII.

Association Between InRCII and EMs

The correlation between InRCII and EMs was analyzed using weighted logistic regression, with results presented in Table 2. When analyzing InRCII as a continuous variable, we observed increased EMs risk with rising InRCII across all three models (Unadjusted model: OR = 1.200, 95% CI [1.090, 1.321], $P = 0.001$; Partially adjusted model: OR = 1.203, 95% CI [1.088, 1.330], $P = 0.001$; Fully adjusted model: OR = 1.250, 95% CI [1.070, 1.461], $P = 0.006$). This association remained statistically significant after converting InRCII to categorical tertiles. In the fully adjusted model, individuals in T3 exhibited a 120.6% higher likelihood of developing EMs (OR = 2.206, 95% CI [1.266, 3.845], $P = 0.007$). Additionally, the trend test showed statistical significance (P for trend = 0.006). Restricted cubic spline analysis in Figure 3 further revealed a linear positive correlation between InRCII and EMs (P overall = 0.001; P for non-linearity = 0.239).

Subgroup Analysis

We conducted subgroup studies to evaluate the stability of the relationship between InRCII and EMs across different populations. As shown in Figure 4, the results indicate that the positive correlation between InRCII and EMs persists

**Figure 3** Dose-Response Relationship Between InRCII and EMs.

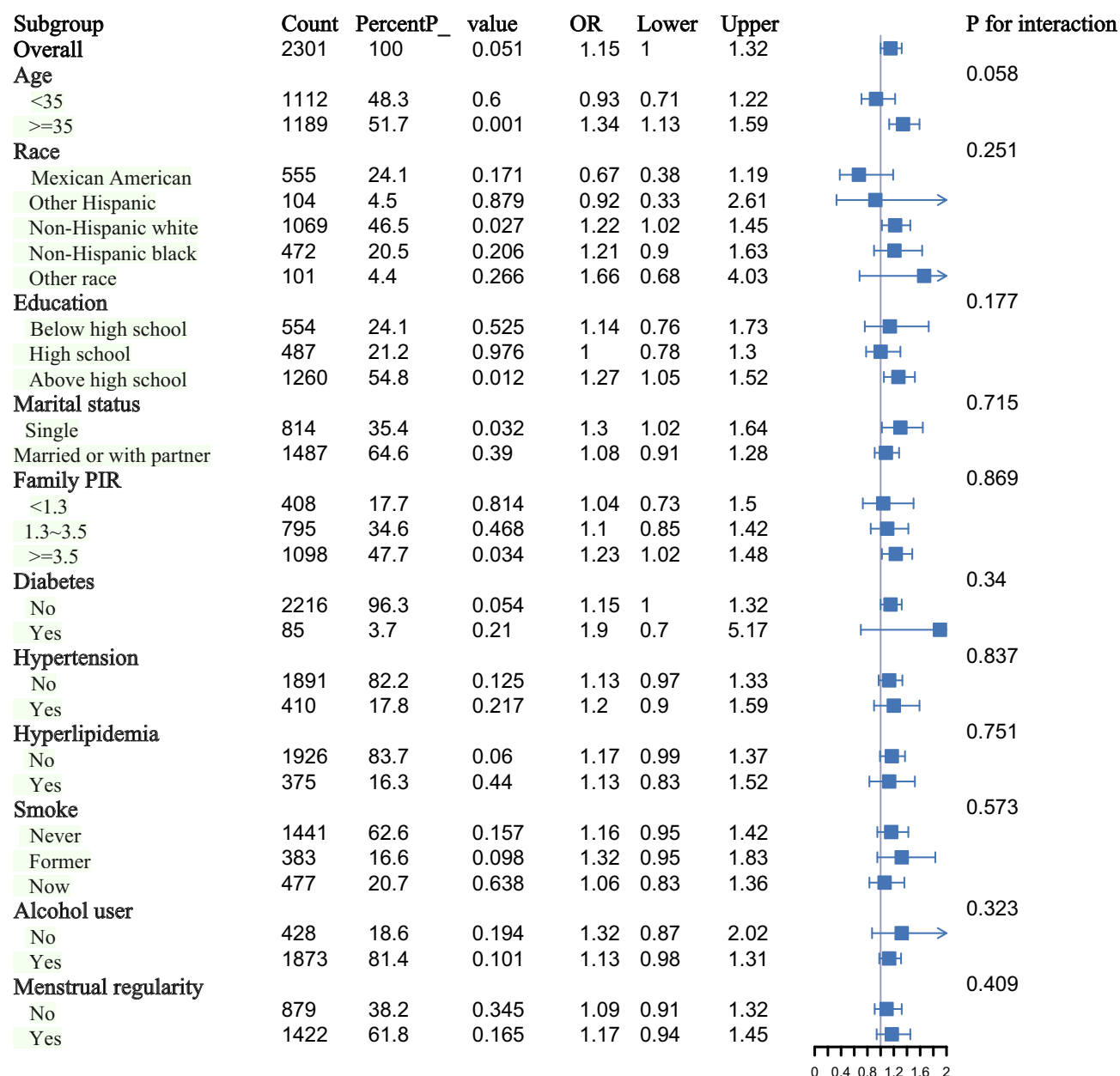


Figure 4 Forest plot of subgroup analysis for relationships between lnRCII and EMs.

regardless of stratification by age, race, education level, income, marital status, smoking, alcohol consumption, hypertension, hyperlipidemia, diabetes, or menstrual regularity (P for interaction > 0.05).

Construction of Predictive Models

In this study, LASSO regression was employed to screen for significant variables. As illustrated in Figure 5, 15 variables were ultimately identified: age, race, education level, marital status, family income level, fasting glucose, insulin, triglycerides, smoking status, alcohol consumption, diabetes, hyperlipidemia, age at menarche, and menstrual regularity. Based on these 15 identified risk factors, a nomogram was developed in Figure 6. By summing the points corresponding to each variable characteristic, the probability of EMs occurrence can be estimated.

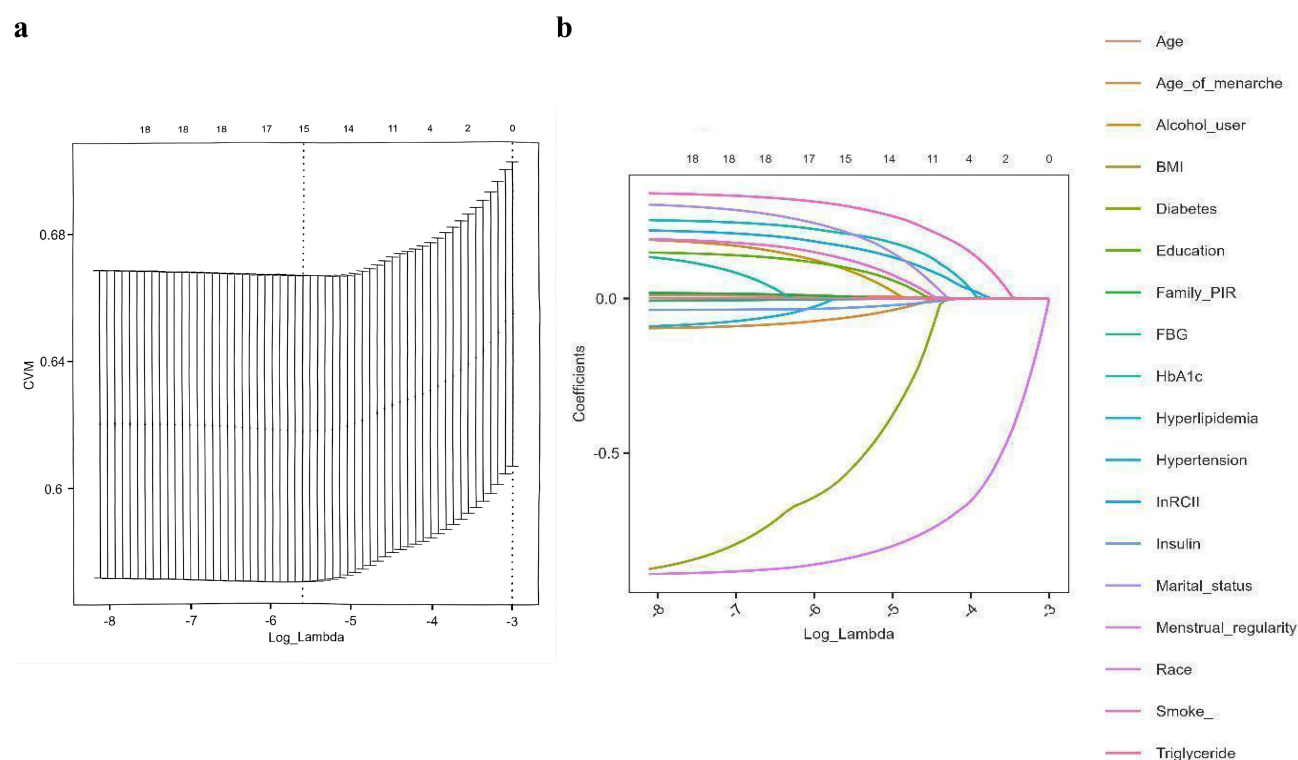


Figure 5 LASSO penalized regression analysis was used to identify factors associated with EMs (a) Cross Validation Error (CVM) plot for different Log Lambda values. (b) The coefficient trajectory for each variable as Log Lambda changes.

Discussion

This study involving 2,316 participants demonstrates a significant positive association between InRCII and EMs. In particular, a 25% increased risk of EMs was linked to every 1-standard-deviation rise in InRCII, and this relationship remained independent of other risk factors. RCS analysis revealed a linear association between InRCII and EMs. Subgroup analysis demonstrated the stability of this association across diverse populations. Relevant variables were then screened using the LASSO regression model. Using the significant factors that were found, a nomogram prediction model was constructed. This model is not merely a simple statistical tool. First, the key variables included in this nomogram were selected through LASSO regression, which helps avoid directly incorporating a large number of potentially irrelevant or collinear variables into the final model. Second, InRCII remained in the model after LASSO screening, providing preliminary evidence that it is an independent influencing factor for endometrioma even when numerous competing factors are considered. Furthermore, this model quantifies the independent contribution of each screened risk factor. Most importantly, the nomogram visualizes the complex regression equation, allowing clinicians or researchers to assign points based on specific variable values of individual patients (such as InRCII level, age, etc.) and intuitively observe the predicted probability of EMs for that individual. This significantly enhances the model's interpretability and potential convenience for clinical application.

EMs is a gynecological disorder characterized by estrogen dependency and chronic inflammatory features. Its fundamental pathology manifests as functional endometrial tissue occurring outside the uterine cavity, such as in the ovaries, fallopian tubes, and peritoneum.³⁰ Its development may involve interactions among multiple contributing factors. Before this, numerous studies utilizing the NHANES database have investigated risk factors associated with EMs. Results consistently demonstrate that inflammation and metabolism play crucial roles in the pathogenesis and progression of EMs. For instance, Chen et al revealed an association between EMs and remnant cholesterol (RC), advising that cholesterol metabolism status should be monitored in EMs patients.¹⁵ The dietary inflammatory index and EMs were found to be related by Hu et al, indicating that non-pharmacological methods may lessen or enhance EMs symptoms.³¹ Consequently, the RCII, which integrates markers of cholesterol metabolism and inflammation, not only

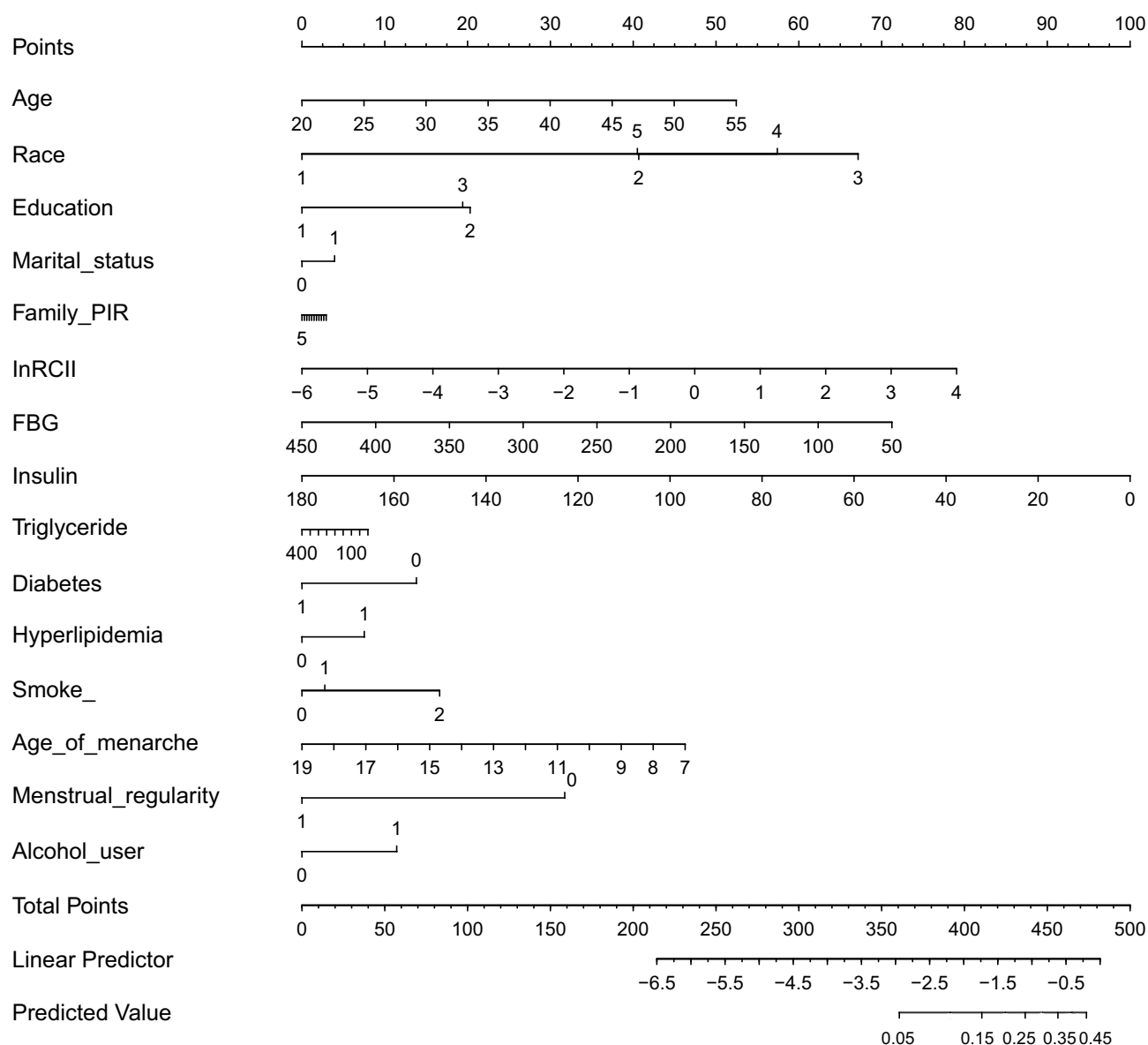


Figure 6 Nomograms for EMs risk prediction.

reflects lipid metabolic imbalance but also serves as a composite index of chronic inflammatory status. It likely possesses stronger predictive capability than individual lipid or inflammatory markers and has been employed to assess risks for cardiovascular diseases.^{22,27} The results of this investigation confirm that lnRCII is a reliable risk biomarker for EMs. Although lnRCII may serve as a promising biomarker for predicting EMs, the specific biological mechanisms underlying this association remain incompletely understood. According to current research, the observed positive association between lnRCII levels and EMs can be explained by several possible processes. These mechanisms primarily involve ectopic endometrial implantation and invasiveness, local and systemic inflammatory microenvironments, hormonal dysregulation (eg, estrogen hypersensitivity), immune evasion accompanied by reduced natural killer cell activity, and neuroendocrine dysfunction.^{32–37}

Studies indicate that both cholesterol metabolism and inflammatory responses play crucial roles in numerous pathological conditions, particularly in autoimmune and endocrine-related disorders. Literature reports that peritoneal fluid from EMs patients is rich in inflammatory cytokines (eg, IL-1 β , IL-6, TNF- α), chemokines (eg, MCP-1, RANTES), oxidative stress products, and bioactive lipid molecules (eg, prostaglandins).²⁵ These substances participate in local

endometrial cell adhesion, invasion, angiogenesis and neurogenesis.³⁸ Research indicates that abnormal cholesterol metabolism may influence the development of endometriosis by promoting chronic inflammation.³⁹ For instance, cholesterol accumulation can activate the immune system, triggering cytokine release and thereby exacerbating inflammatory responses.^{40,41} This occurs because cholesterol metabolism disorders affect the functionality of macrophages, dendritic cells, and NK cells, impairing their ability to recognize and clear ectopic endometrial cells.⁴² Animal experiments further demonstrate that endometrial lesions in the peritoneal cavity of high-fat diet mice were larger than those in normal-diet controls.⁴³ Immunohistochemistry revealed extensive infiltration of macrophages within the lesions, accompanied by abundant oxidized lipid deposits.^{44,45} Cholesterol serves as a key precursor for steroid hormone synthesis, such as estrogen. In EMs patients, the inflammatory microenvironment induces increased aromatase activity, which facilitates the metabolism of cholesterol into estrogen.⁴⁶ This process activates the ERK1/2 signalling pathway, thereby promoting the proliferation and invasion of ectopic endometrial tissue.⁴⁷ Additionally, non-HDL-C components (such as LDL-C and VLDL-C) are prone to oxidation into oxLDL, and these oxidized forms bind to TLR4 receptors, activating both the NF- κ B signalling pathway and the NLRP3 inflammasome pathway.⁴⁸ Such lipid signalling molecules enhance inflammatory responses and facilitate immune escape within the ectopic lesions of endometriosis.⁴⁹ Decreased HDL-C levels often trigger subsequent inflammation, whereby inflammatory factors (eg, IL-1 β , VEGF) activate vascular endothelial cells and nerve growth factor expression, thereby promoting lesion persistence.^{50,51} In summary, elevated RCII levels indicate a state of potential immune tolerance in individuals, creating an immunoprotective environment conducive to the implantation, invasion, and sustained survival of endometriotic lesions.

Together, these findings demonstrate the intricate relationship that exists between metabolic dysregulation, inflammation and EMs. RCII provides a more comprehensive risk prediction by combining RC and CRP/hsCRP. The application of machine learning facilitates a thorough evaluation of RCII's predictive performance. From a clinical application perspective, the InRCII addresses critical limitations of existing diagnostic and risk assessment tools. While imaging examinations such as laparoscopy serve as the gold standard, they are invasive, costly, and associated with low patient compliance, making them unsuitable for large-scale screening in the general population. Serum biomarkers like CA125 suffer from insufficient specificity and are susceptible to interference from benign gynecological conditions. In contrast, the lipid and inflammatory indicators involved in the InRCII are readily obtainable, offering the advantages of being non-invasive, low-cost, and easy to perform, thereby demonstrating strong clinical applicability. Based on the findings of this study, which confirmed a significantly elevated risk of disease onset in the high-InRCII group, this index can be applied for primary screening in the general population of women of reproductive age. It enables the rapid identification of high-risk individuals and guides further clinical examinations, thereby improving early diagnosis efficiency and reducing disease burden. Additionally, RCII can be utilized for monitoring therapeutic efficacy and assessing disease progression in EMs. Given the established link between residual cholesterol and cardiovascular risk, our findings suggest that EMs patients with elevated RCII may require concurrent monitoring of their metabolic health. First and foremost, because it is a cross-sectional research, it is unable to determine if higher RCII causes or results from EMs. Secondly, the diagnosis of EMs was obtained from NHANES participants via self-reported questionnaires, which may introduce misinformation. Additionally, we failed to take into consideration confounding variables that may skew the results, such as physical activity and prior pelvic surgery.

Before clinical application, prospective cohort studies are required to further validate the reliability of RCII in predicting endometrioma (EMs) and to evaluate its predictive accuracy, clinical utility, and cost-effectiveness as a potential target for public health interventions. A large-sample, multi-center cohort study could be established to collect RCII levels from diverse populations and EMs patients at different disease stages. This would facilitate the creation of a longitudinal tracking database to clarify relationships between RCII and clinical indicators, including disease severity, pain scores, and recurrence rates. Integrating RCII with biomarkers such as CA125, VEGF, IL-6, and miRNA to establish multi-indicator prediction models can enhance diagnostic specificity and sensitivity. If subsequent validation confirms favourable predictive performance of RCII, consideration could be given to incorporating it into routine gynecological examinations for women, particularly for high-risk populations with a history of dysmenorrhea or infertility.

Conclusion

This cross-sectional investigation shows a strong correlation between the risk of EMs and high RCII levels. And we utilized machine learning methods for model prediction. These findings indicate that RCII holds promise as a potential biomarker for EMs, offering new avenues for future diagnosis, treatment, and personalized risk prediction of EMs with broad application prospects. But large-scale prospective cohort studies are necessary before considering the application of RCII in clinical practice.

Abbreviations

NHANES, National Health and Nutrition Examination Survey; RCII, Remnant Cholesterol Inflammatory Index; EMs, Endometriosis; FPG, Fasting blood-glucose; HbA1c, Glycosylated hemoglobin; PIR, Income to poverty ratio; HDL-C, High-density cholesterol; LDL-C, Low-density lipoprotein cholesterol; CRP, C-reactive protein; LASSO, Least absolute shrinkage and selection operator; RCS, Restricted cubic spline; OR, Odds ratio; CI, Confidential interval; ML, Machine learning.

Data Sharing Statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: <https://www.cdc.gov/nches/nhanes>.

Ethics Approval and Consent to Participate

The study was approved by the Institutional Review Board of the CDC's National Center for Health Statistics, and all participants provided written informed consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All analyses were conducted in accordance with NHANES guidelines (<https://www.cdc.gov/nchs/nhanes/irba98.htm>) with written informed consent given by all participants and ethical approval granted by the NCHS research ethics review board (<https://www.cdc.gov/nchs/nhanes/about/erb.html>).

According to item 1 (conducting research using legally obtained public data or data generated through observation without interfering with public behavior) and 2 (conducting research using anonymized information data) of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China, this research is exempt from ethical review.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Informed Consent Statement

All participants provided informed consent during the data collection process by the NHANES protocol.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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