RESEARCH

Elevated log uric acid-to-high-density lipoprotein cholesterol ratio (UHR) as a predictor of increased female infertility risk: insights from the NHANES 2013–2020

Yanxiang Kong[1†], Miaoling Lin[1†], Yiman Fu[1], Baoyi Huang[1], Mengqi Jin[1] and Lin Ma[1*]

Abstract

Background Infertility is a multifaceted condition influenced by metabolic and biochemical factors. Uric acid (UA) and high-density lipoprotein cholesterol (HDL-C) may individually affect reproductive health. The UA-to-HDL-C ratio (UHR), an emerging indicator of chronic inflammation and metabolic status, may be associated with infertility because of its connections to metabolic disorders, disrupted reproductive processes, and other related factors. Nevertheless, evidence of the relationship between the UHR and infertility remains limited and controversial. Therefore, potential associations were analyzed in this study.

Methods In this cross-sectional study, data from the 2013–2020 National Health and Nutrition Examination Survey (NHANES) were utilized, a nationally representative survey assessing the health and nutritional status of the U.S. population. Female participants aged 18–45 years ($n = 6502$) whose infertility status was determined through self-reported responses to reproductive health questions were included. The primary outcome was infertility, defined on the basis of responses indicating difficulty in conceiving over the past year. Between-group differences were analyzed via Student's t test or the Mann–Whitney U test for continuous variables or the chi-square test for categorical data. The independent association between infertility status and the log UHR was assessed by log computes logarithms by default natural logarithms. Subgroup analyses were performed to assess the strength of the results.

Results The mean log UHR of the women in the infertility group was significantly greater than that of the women in the noninfertility group (5.34 vs. 5.22, $P < 0.001$). Adjusted analyses revealed that an increase in the log UHR was associated with greater odds of infertility (odds ratio (OR) = 1.830, 95% confidence interval (CI) 1.396–2.401). Subgroup analysis revealed that women younger than 35 years with an elevated log UHR faced an even greater risk of infertility (OR = 2.716, 95% CI 1.784–4.162; $P < 0.001$).

[†]Yanxiang Kong and Miaoling Lin contributed equally to this work and share first authorship.

*Correspondence:
Lin Ma
malin8@mail.sysu.edu.cn

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

Conclusions An elevated UHR is associated with a higher risk of infertility, and this knowledge may be beneficial for developing a nonpharmacological intervention for improving fertility outcomes. Further research is needed to clarify the direct impact of the UHR on female infertility, which could inform future strategies for prevention and treatment.

Keywords HDL cholesterol, Uric acid, Infertility, National health and nutrition examination survey

Background

Infertility is defined as the inability to conceive during childbearing years, despite having regular, unprotected intercourse for at least 12 months. Infertility has emerged as a substantial public health challenge that impacts approximately 8 to 15% of couples in their reproductive years worldwide, resulting in substantial emotional and economic burdens [1, 2]. Recent research highlights the role of metabolic imbalances as contributors to infertility, and there has been particular interest in the uric acid (UA)-to-high-density lipoprotein cholesterol (HDL-C) ratio (UHR); the UHR may provide insight into reproductive health, as it reflects both inflammatory and metabolic status. Managing metabolic health in infertile women presents unique challenges; despite the increasing awareness of these factors, comprehensive biomarkers that integrate metabolic and inflammatory status to guide diagnosis and treatment strategies are lacking.

The UHR involves a combination of inflammatory and metabolic status indicators, reflecting the combined effect of UA and HDL-C levels on reproductive health. A high UHR may increase the risk of infertility, especially in cases linked to metabolic and inflammatory imbalances. On the one hand, UA, a metabolite from purine breakdown, is linked to metabolic syndrome and recognized as an inflammatory marker that is potentially disruptive to reproductive functions. Studies suggest that elevated UA levels may increase the risk of poor ovarian response and infertility, likely through oxidative stress, inflammation, and endothelial dysfunction [3]. On the other hand, HDL-C plays an important role in lipid metabolism and cardiovascular health while significantly influencing reproductive outcomes. Clinical studies indicate that lower HDL-C levels increase infertility risk through multiple mechanisms, specifically by regulating reproductive hormonal balance, endometrial receptivity, and ovarian function [4–6].

The UHR has emerged as a promising marker with superior evaluative capabilities in individuals with conditions such as metabolic syndrome, coronary artery disease, hypertension [7–11], age-related diseases, and mortality across diverse populations, highlighting its potential in clinical risk assessment and management [12–15]; additionally, the UHR may provide a more comprehensive understanding of metabolic status and its potential influence on reproductive function. In particular, a high ratio could suggest an imbalance in oxidative stress and lipid metabolism, which might interfere with the complex processes involved in conception and pregnancy. For example, the ratio could indicate that hormonal regulation, ovarian function, and endometrial quality are atypical. Although the potential of the UHR in evaluating metabolic status is well documented, its role as a predictive tool for infertility remains unclear. The focus of research has been primarily on the individual effects of UA and HDL-C levels on reproductive health, and the UHR in infertile populations has been specifically investigated in only a few studies. This gap underscores the need for further exploration of the clinical relevance of the UHR in female infertility.

The hypothesis of this study was that an elevated log UHR is linked to a greater risk of infertility in women. Therefore, this study was performed on the basis of 2013–2020 National Health and Nutrition Examination Survey (NHANES) data. Understanding the relationships among UA levels, HDL-C levels, and infertility could pave the way for the development of novel diagnostic and therapeutic approaches for couples struggling with infertility.

Materials and methods
Materials and methods

In this study, data from the NHANES, a nationally representative cross-sectional survey conducted by the National Center for Health Statistics (NCHS), were utilized. The NHANES uses a multistage probability sampling design to evaluate the health and nutritional status of the noninstitutionalized population in the United States. A cross-sectional design was chosen for its efficiency in capturing health-related variables and associations at a specific time point, making it ideal for analyzing large-scale population datasets such as the NHANES population. Unlike longitudinal studies, which track participants over time to explore trends or causality, cross-sectional studies provide a cost-effective and timely approach to identifying associations. All NHANES protocols were approved by the NCHS Research Ethics Review Board, and written informed consent was obtained from all participants.

Female participants aged 18–45 years from the 2013–2020 NHANES cycles ($n = 6502$) were initially included. Participants with missing data on infertility status ($n = 978$), HDL-C levels ($n = 327$), UA levels ($n = 17$), or other key covariates ($n = 1009$) were excluded; the remaining participants composed the final sample for analysis.

Exposure: log uric acid-to-high-density lipoprotein cholesterol

Fasting blood samples were used to measure UA and HDL-C levels. The log-transformed UHR (log UHR) [16] was calculated by dividing the natural logarithm of UA (µmol/L) by that of HDL-C (mmol/L).

Outcome: infertility

Infertility status was assessed with a reproductive health questionnaire. The participants were classified as infertile if they answered "yes" to the following question: "Have you tried to become pregnant for at least a year without becoming pregnant?"

Covariates

The following covariates [7, 8] were selected on the basis of their potential to influence the relationship between the log UHR and infertility risk: age (<35 years, ≥35 years); race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, other); marital status (married, other); educational level (below high school, high school, above high school); lifestyle factors, including smoking status (never, former, current) and alcohol consumption status (never, former, current); anthropometric variables, including body mass index (BMI; <25, 25–30, ≥30 kg/m²); and clinical indicators, including hypertension status (yes, no), diabetes status (yes, no), alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels, creatinine levels, and blood urea nitrogen levels.

Statistical analysis

The participants were divided into infertile and fertile groups. The Shapiro–Wilk test was conducted to assess the normality of the continuous variables. Continuous variables are expressed as the means ± standard deviations (SDs) and were analyzed via Student's t test or the Mann–Whitney U test. Variables that did not meet normality assumptions are presented as medians with interquartile ranges. Categorical variables are expressed as percentages and were analyzed via the chi-square test. The independent association between the log UHR and infertility risk was assessed through multivariable logistic regression models. Multicollinearity among independent variables was assessed using variance inflation factor (VIF) analysis. A threshold of VIF < 10 was used to indicate the absence of significant multicollinearity. All the variables in the model demonstrated VIF values well below this threshold, confirming the robustness of the regression analysis. The crude model was unadjusted; Model 1 was adjusted for age, race, marital status, educational level, and BMI; and Model 2 was further adjusted for smoking status, alcohol consumption status, hypertension status, diabetes status, ALT levels, AST levels, creatinine levels, total cholesterol levels and blood urea nitrogen levels. The log UHR was analyzed as both a continuous variable and a categorical variable (quartiles, a statistical method of dividing data into four equal parts, which not only facilitates the analysis of continuous variables but also provides a clearer perspective for identifying patterns and trends) [17, 18]. Considering that clinical indicators and outcomes are usually not simple linear relationships, restricted cubic spline (RCS) analysis [19, 20], a segmented polynomial method, was used to assess nonlinear relationships between the log UHR and infertility risk. This approach ensures the smoothness of the curve, making the data fit closer to the true association curve, which is better suited to improving predictive performance. Subgroup analyses and interaction tests were conducted to explore the effects of covariates on the associations. All analyses were performed via R version 4.3.1, with $P < 0.05$ (two-tailed) considered to indicate statistical significance.

Results

Baseline characteristics of the study participants

In total, 4171 participants were included in the analysis, 3621 of whom were categorized as fertile and 550 of whom were categorized as infertile on the basis of their responses to the reproductive health questionnaire (Fig. 1). The baseline characteristics of the two groups are summarized in Table 1. Significant differences between the infertile and fertile groups were observed across multiple variables. The women in the infertility group were, on average, older (36 vs. 33 years, $P < 0.001$) and had higher rates of smoking, obesity, hypertension, and diabetes ($P < 0.001$ for all). Additionally, infertile participants had elevated levels of UA ($P < 0.001$) and total cholesterol ($P = 0.026$), along with reduced HDL-C levels ($P < 0.001$). The log UHR values were notably higher in the infertility
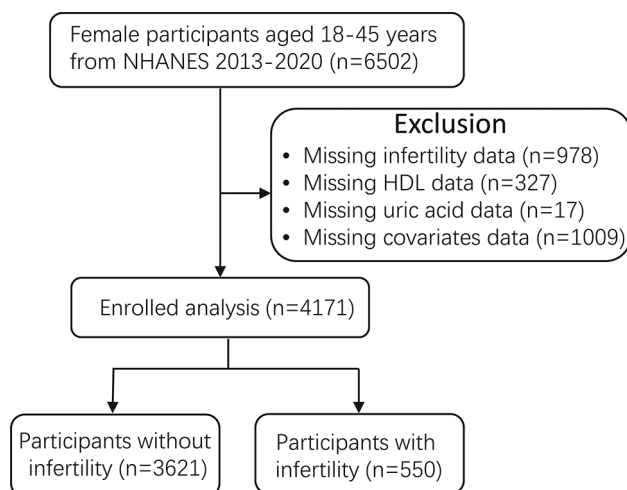
Fig. 1 Flow chart of participant inclusion

Table 1 Baseline characteristics of the participants

Variables	Total (n = 4171)	Non-infertility (n = 3621)	Infertility (n = 550)	P
Age, years	33.00 [26.00, 40.00]	33.00 [26.00, 39.00]	36.00 [30.00, 41.00]	< 0.001
Age				< 0.001
< 35 years	2318 (55.57)	2069 (57.14)	249 (45.27)	
≥ 35 years	1853 (44.43)	1552 (42.86)	301 (54.73)	
Race				0.235
Non-Hispanic White	1375 (32.97)	1173 (32.39)	202 (36.73)	
Non-Hispanic Black	942 (22.58)	821 (22.67)	121 (22.00)	
Mexican-American	692 (16.59)	607 (16.76)	85 (15.45)	
Other	1162 (27.86)	1020 (28.17)	142 (25.82)	
Marital status				< 0.001
Married	36,345 (56.22)	1955 (53.99)	390 (70.91)	
Other	1826 (43.78)	1666 (46.01)	160 (29.09)	
Educational level				0.829
Below high school	612 (14.67)	532 (14.69)	80 (14.55)	
High school or equivalent	787 (18.87)	678 (18.72)	109 (19.82)	
Above high school	2772 (66.46)	2411 (66.58)	361 (65.64)	
Smoking status				0.001
Never	2955 (70.85)	2601 (71.83)	354 (64.36)	
Former	458 (10.98)	390 (10.77)	68 (12.36)	
Current	758 (18.17)	630 (17.40)	128 (23.27)	
Alcohol consumption status				0.057
Never	623 (14.94)	554 (15.30)	69 (12.55)	
Former	155 (3.72)	127 (3.51)	28 (5.09)	
Current	3393 (81.35)	2940 (81.19)	453 (82.36)	
BMI, kg/m^2	28.30 [23.40, 34.40]	28.00 [23.20, 33.80]	30.75 [24.60, 37.30]	< 0.001
BMI	1385 (33.21)	1232 (34.02)	153 (27.82)	< 0.001
< 25 kg/m^2	1003 (24.05)	903 (24.94)	100 (18.18)	
25–30 kg/m^2	1783 (42.75)	1486 (41.04)	297 (54.00)	
≥ 30 kg/m^2	623 (14.94)	554 (15.30)	69 (12.55)	
Hypertension				< 0.001
No	3450 (82.71)	3027 (83.60)	423 (76.91)	
Yes	721 (17.29)	594 (16.40)	127 (23.09)	
Diabetes				0.003
No	3845 (92.18)	3356 (92.68)	489 (88.91)	
Yes	326 (7.82)	265 (7.32)	61 (11.09)	
ALT, U/L	15.00 [12.00, 20.00]	15.00 [12.00, 20.00]	16.00 [13.00, 22.00]	0.050
AST, U/L	18.00 [16.00, 22.00]	18.00 [16.00, 22.00]	18.00 [15.00, 22.00]	0.310
Creatinine (µmol/L)	61.88 [54.81, 69.84]	61.88 [54.81, 69.84]	63.20 [55.69, 69.84]	0.948
Blood urea nitrogen (µmol/L)	3.93 [3.21, 4.64]	3.93 [3.21, 4.64]	3.93 [3.21, 5.00]	0.833
Uric acid (µmol/L)	261.70 [226.00, 309.30]	261.70 [220.10, 303.30]	279.60 [232.00, 325.62]	< 0.001
Total cholesterol (mmol/L)	4.55 [4.01, 5.15]	4.53 [4.01, 5.15]	4.59 [4.07, 5.25]	0.026
HDL-C (mmol/L)	1.40 [1.16, 1.68]	1.40 [1.16, 1.68]	1.32 [1.09, 1.58]	< 0.001
Log UHR	5.24 (0.41)	5.22 (0.41)	5.34 (0.41)	< 0.001
Log UHR				< 0.001
Q1	1043 (25.01)	949 (26.21)	94 (17.09)	
Q2	1045 (25.05)	915 (25.27)	130 (23.64)	
Q3	1037 (24.86)	890 (24.58)	147 (26.73)	
Q4	1046 (25.08)	867 (23.94)	179 (32.55)	

BMI, body mass index; ALT, aspartate aminotransferase; AST, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; UHR, uric acid-to-HDL-C ratio; log UHR quartile range: Q1: 3.99,4.95; Q2: 4.96,5.23; Q3: 5.24,5.50; Q4: 5.51,6.83

group than in the noninfertility group ($P < 0.001$). These findings suggest that metabolic and demographic factors differ significantly between women with and women without infertility, highlighting the potential relevance of the log UHR as a biomarker.

Furthermore, variables such as race, educational level, alcohol consumption status, and ALT, AST, creatinine, and blood urea nitrogen levels were not significantly different between the groups ($P > 0.05$).

Associations between the log uric acid-to-high-density lipoprotein cholesterol and infertility risk

The VIF analysis indicated no significant multicollinearity among the independent variables, with all values being less than 10. The association between the log UHR and infertility risk was assessed via multiple logistic regression analysis. As shown in Table 2, the log UHR was significantly positively correlated with infertility risk across all the models.

According to the crude model, the odds ratio (OR) was 2.048 (95% confidence interval (CI): 1.642–2.557, $P < 0.001$), indicating a strong association. After adjusting for age, race, marital status, educational level, and BMI in Model 1, the positive relationship remained significant (OR = 1.854, 95% CI: 1.432–2.405, $P < 0.001$). Model 2 was further adjusted for smoking status, alcohol consumption status, hypertension status, diabetes status, alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels, creatinine levels, total cholesterol levels, and blood urea nitrogen levels (OR = 1.830, 95% CI: 1.396–2.401, $P < 0.001$).

When the log UHR was categorized into quartiles, participants with a UHR in the highest quartile presented a greater risk of infertility than did those with a UHR in the lowest quartile according to fully adjusted Model 2 (OR = 1.701, 95% CI: 1.246–2.331, $P < 0.001$). This consistent association was further supported by RCS analysis, which revealed a linear increase in infertility risk as the log UHR increased (Fig. 2). These findings suggest

that a higher log UHR is independently associated with an increased risk of infertility. Early identification of elevated log UHR levels in women undergoing fertility treatments could facilitate the provision of timely and targeted interventions.

Subgroup analysis

Subgroup analyses were performed to evaluate the consistency of the association between the log UHR and infertility across various demographic and clinical subgroups (Table 3). Interaction tests were conducted to determine whether the relationship between the log UHR and infertility risk was influenced by covariates.

The results indicated that age significantly modified the association ($P < 0.001$). Among women younger than 35 years, the relationship was notably stronger, with an OR of 2.716 (95% CI: 1.784–4.162), indicating an increased risk of infertility in this group. This suggests that younger women with higher log UHR values may represent a particularly vulnerable population, potentially requiring targeted interventions.

The absence of significant interactions for covariates such as race, marital status, educational level, smoking status, alcohol consumption status, BMI, hypertension status, and diabetes status ($P > 0.05$) suggests that the association between the log UHR and infertility risk remains consistent across these diverse subgroups. However, the association appeared slightly more pronounced among non-Hispanic white and black women, married individuals, individuals with higher educational levels, current smokers and drinkers, individuals with a BMI of either <25 kg/m² or ≥30 kg/m², and individuals without hypertension or diabetes. However, the lack of statistical significance suggests that these variations were not substantial enough to modify the overall relationship.

These findings suggest that the log UHR is a robust marker of infertility risk across diverse subgroups, with age being a significant modifier. The stronger association observed in younger women underscores the need for

Table 2 Logistic regression analysis of the association between the log UHR and infertility risk

	Crude model	P	Model 1[a]	P	Model 2[b]	P
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
Log UHR (continuous)	2.048 (1.642,2.557)	< 0.001	1.854 (1.432,2.405)	< 0.001	1.830 (1.396,2.401)	< 0.001
Log UHR (categories)						
Q1	Ref.		Ref.		Ref.	
Q2	1.434 (1.085,1.903)	0.012	1.433 (1.078,1.911)	0.014	1.444 (1.084,1.929)	0.012
Q3	1.667 (1.270,2.200)	< 0.001	1.534 (1.150,2.054)	0.004	1.526 (1.140,2.051)	0.005
Q4	2.084 (1.602,2.728)	< 0.001	1.759 (1.301,2.388)	<0.001	1.701 (1.246,2.331)	<0.001
P for trend		< 0.001		< 0.001		0.002

OR, odds ratio; CI, confidence interval

[a]Model 1: adjusted for age, race, marital status, educational level, and BMI

[b]Model 2: Model 1 + smoking status, alcohol consumption status, hypertension status, diabetes status, ALT levels, AST levels, creatinine levels, total cholesterol levels, and blood urea nitrogen levels
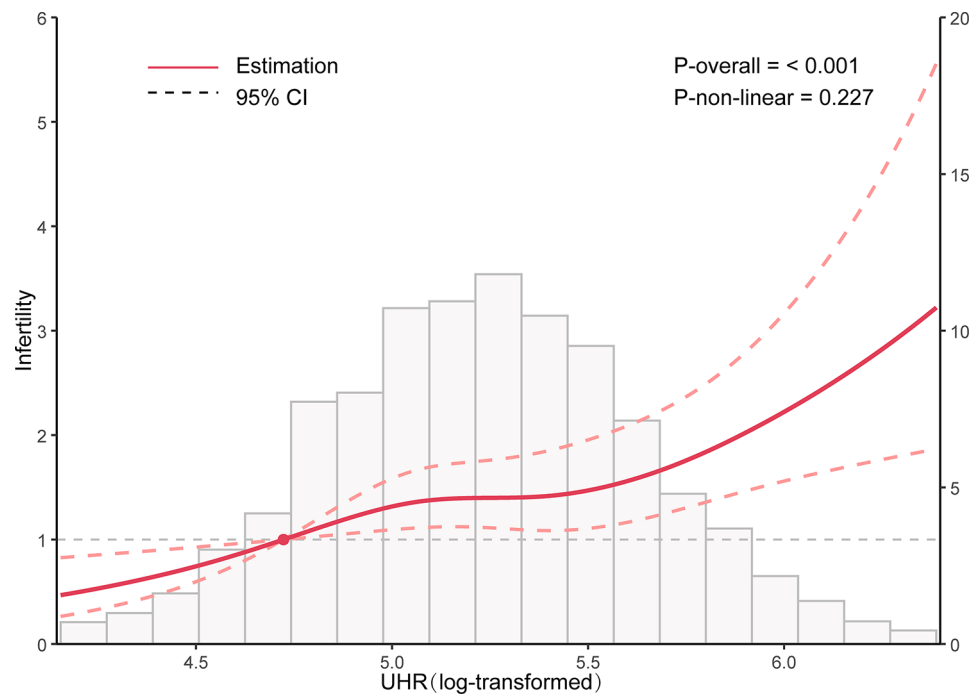
Fig. 2 Restricted cubic spline analysis of the relationship between the log UHR and infertility status

early identification and management of metabolic and lipid-related risks in this population to mitigate infertility risk effectively.

Discussion

In this cross-sectional study, it was found that women with infertility had significantly higher log UHR values than those without infertility. Multivariate regression analyses demonstrated a consistent positive association between the log UHR and infertility risk, with a linear trend indicating that a higher log UHR was linked to an increased risk of infertility. These findings highlight the potential of the log UHR as a marker for infertility risk, underscoring the importance of metabolic health management in reproductive planning.

Female infertility is a condition with a complex etiology and is influenced by multiple biological mechanisms and pathways. Notably, female fertility is highly dependent on the successful regulation of energy metabolism. Metabolic disturbances have clinically important consequences for human reproduction [21].

Compared with the evaluation of HDL-C and UA levels separately, the UHR has superior evaluative capabilities and is a recently proposed novel index of metabolism and inflammation, such as that observed in individuals with metabolic syndrome, type 2 diabetes mellitus, Hashimoto's thyroiditis, coronary artery disease, and hypertension [7–11]. This is the only study in which indirect evidence of a connection was obtained. The association between the UHR and infertility can be attributed to its

reflection of underlying disruptions in oxidative stress and lipid metabolism, both of which are critical to reproductive function. The study revealed a significant association between an elevated log UHR and an increased risk of infertility, suggesting that an imbalance in oxidative stress and lipid metabolism may contribute to impaired fertility. The two major components of the UHR, namely, UA and HDL-C levels, may be involved in the pathophysiological mechanisms related to infertility.

These results suggest that the log UHR is positively related to infertility, indicating that lowering the log UHR may help decrease the risk of infertility. It was hypothesized that the mechanism by which a higher UHR increases the risk of infertility may be related to the following two factors.

On the one hand, UA, as both an antioxidant and a prooxidant, may contribute to female reproductive disorders through mechanisms such as oxidative stress, inflammation, and mitochondrial dysfunction [22–24]. High UA levels can increase reactive oxygen species (ROS) production, activate inflammatory pathways such as the MCP-1 and NF-κB pathways, damage reproductive tissues, and impair follicular development and sperm quality [25, 26]. Elevated UA levels are also linked to chronic low-grade inflammation, which is associated with infertility risk, particularly in individuals with conditions such as polycystic ovary syndrome (PCOS), for whom elevated UA levels contribute to insulin resistance and anovulatory infertility [27–29]. The study revealed that UA and total cholesterol levels were higher in infertile women than in

Table 3 Results of the subgroup analyses

Variables	OR	95% CI	P	P for interaction
Age				< 0.001
< 35 years	2.716	1.784,4.162	< 0.001	
≥ 35 years	1.431	1.002,2.049	0.049	
Race				0.190
Non-Hispanic White	1.951	1.219,3.141	0.006	
Non-Hispanic Black	2.873	1.575,5.313	0.001	
Mexican-American	1.461	0.733,2.939	0.283	
Other	1.477	0.847,2.582	0.170	
Marital status				0.526
Married	1.664	1.197,2.318	0.003	
Other	2.403	1.481,3.924	< 0.001	
Educational level				0.540
Below high school	0.680	0.312,1.469	0.329	
High school or equivalent	2.239	1.186,4.296	0.014	
Above high school	2.096	1.500,2.938	< 0.001	
Smoking status				0.204
Never	1.979	1.399,2.806	< 0.001	
Former	1.933	0.862,4.386	0.111	
Current	2.084	1.186,3.706	0.011	
Alcohol consumption status				0.874
Never	1.100	0.463,2.603	0.828	
Former	1.451	0.244,8.902	0.682	
Current	2.018	1.502,2.717	< 0.001	
BMI				0.381
< 25 kg/m^2	2.618	1.488,4.641	0.001	
25–30 kg/m^2	1.415	0.766,2.62	0.268	
≥ 30 kg/m^2	1.988	1.341,2.963	0.001	
Hypertension				0.070
No	2.030	1.483,2.785	< 0.001	
Yes	1.324	0.760,2.325	0.324	
Diabetes				0.537
No	1.941	1.452,2.600	< 0.001	
Yes	1.509	0.647,3.577	0.343	

Adjustments were made for age, race, marital status, educational level, smoking status, alcohol consumption status, BMI, hypertension status, diabetes status, ALT levels, AST levels, creatinine levels, total cholesterol levels and blood urea nitrogen levels. No adjustments were made for stratified variables in the subgroup analysis

noninfertile women, which is consistent with the findings of previous studies. However, while these associations are being explored, the direct effect of UA levels on female fertility remains to be fully elucidated.

On the other hand, research has shown that disrupted HDL-C metabolism negatively impacts female fertility. HDL-C is the only lipoprotein found in significant amounts in follicular fluid, and its size and composition are linked to embryo quality. Cholesterol accumulation within cells can affect oocyte viability by altering calcium channels and disrupting cell survival pathways [30]. Additionally, HDL-C may influence fertility through its effects on hormonal balance, particularly by interacting with sex hormone-binding globulin (SHBG) and affecting hormone availability [31]. Miettinen reported that SR-BI knockout mice with abnormal HDL-C levels were infertile [32], whereas Zhuang et al. [33] linked increased

visceral fat to infertility risk. However, Zhu et al. [34] reported no significant association between HDL-C levels and female infertility risk on the basis of genetic data from two large databases. While some studies suggest a lack of a significant association between HDL-C levels and infertility risk, these findings show lower HDL-C levels in infertile women, supporting the hypothesis that metabolic changes, including those in HDL-C metabolism, can impair reproductive health.

Overall, elevated UA levels contribute to oxidative stress, damage oocyte DNA, impair oocyte quality, reduce fertilization rates, and compromise embryo development. Oxidative stress also disrupts folliculogenesis, hormonal balance, and endometrial receptivity by altering key implantation proteins such as integrins and cytokines. Low HDL-C levels diminish the effects of oxidative stress and inflammation, exacerbating UA-induced

oxidative damage. The UHR integrates these factors, with a high UHR reflecting oxidative stress and disrupted lipid metabolism. This imbalance creates an unfavorable environment for fertility, affecting egg quality, ovarian function, and uterine receptivity, ultimately hindering conception and pregnancy.

By identifying individuals with high UHR, doctors may be able to detect early signs of metabolic disturbances and oxidative stress, enabling the use of more targeted interventions to improve fertility outcomes. Potential therapeutic approaches might include antioxidant supplementation, lifestyle modifications (such as diet and exercise), and pharmacological treatments to normalize lipid metabolism and reduce oxidative damage.

The present study revealed a significant association between the log UHR and infertility risk. These findings align with the hypothesis that metabolic alterations may adversely affect reproductive capabilities. The log UHR could be integrated into infertility management protocols as a routine screening marker, particularly for women with concurrent metabolic or immune abnormalities. Early identification of women with elevated log UHR levels and regular monitoring of changes in the log UHR in women undergoing fertility treatments may enable timely interventions, including nonpharmacological approaches such as lifestyle modifications, dietary adjustments, and physical activity, to optimize metabolic health and improve pregnancy outcomes. Future research should prioritize exploring the predictive value of the log UHR across diverse populations, the correlation of the UHR with various infertility symptoms, the long-term effects of an elevated log UHR, the underlying mechanisms linking the UHR to infertility, and the potential benefits of metabolic-targeted interventions. This approach provides a more comprehensive understanding of its clinical significance and utility.

Longitudinal studies with larger sample sizes and more comprehensive assessments of confounding factors could provide more definitive answers. Additionally, understanding the underlying relationships by which the log UHR influences infertility could lead to the development of novel therapeutic strategies for infertility treatment and the establishment of evidence-based guidelines for managing UHR in the context of reproductive health.

Strengths and limitations

This study has several strengths. First, its objectivity and credibility were ensured by the use of data from the NHANES, a nationally representative survey conducted with standardized protocols. Second, the inclusion of multiple covariates helped reduce potential sources of confounding, thereby enhancing the robustness of the findings. Finally, the large, nationally representative

sample size further increased the reliability and generalizability of the results.

A limitation of the study is that the cross-sectional approach prevents the establishment of causality [35], and the retrospective nature of the questionnaire may lead to inaccuracies in self-reported data. Reliance on self-reported infertility data can lead to biases such as recall bias, where participants may misremember or underreport their infertility history, and social desirability bias, where stigma surrounding infertility might result in incomplete or misleading responses. Additionally, heterogeneous interpretations of infertility by respondents could lead to inconsistencies in clinical definitions. Moreover, the absence of male-specific information in the questionnaire introduces the potential for unaccounted confounding factors related to male infertility. Another limitation is the relatively small sample size, which may limit the generalizability of the findings to the broader population. While an association between the log UHR and infertility risk was identified in this study, the underlying mechanisms remain unclear. In future studies, researchers should include larger and more diverse cohorts and use longitudinal or experimental designs to gain a deeper understanding of these relationships.

Conclusions

An elevated log UHR is significantly associated with an increased risk of infertility in women, highlighting the critical link between metabolic health and reproductive outcomes, which is consistent with the hypothesis. The log UHR could serve as a valuable biomarker for identifying women at greater risk of infertility and may be beneficial for developing early intervention and personalized care strategies for improving fertility outcomes.

The findings suggest that UHR can enhance fertility treatment by guiding interventions, improving patient outcomes, and optimizing reproductive health management. Integrating UHR into clinical practice may directly impact patient care and fertility success. In summary, the UHR is a promising biomarker and therapeutic target for improving reproductive health outcomes.

Abbreviations

NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
BMI	Body Mass Index
ALT	Aspartate aminotransferase
AST	Alanine aminotransferase
UA	Uric Acid
HDL-C	High-Density Lipoprotein Cholesterol
UHR	Uric acid-to-High-density lipoprotein cholesterol Ratio
OR	Odds Ratio
CI	Confidence Interval
ROS	Reactive Oxygen Species
MCP-1	Monocyte Chemotactic Protein-1
NF-κB	Nuclear Factor kappa B
SHBG	Sex Hormone-Binding Globulin
KO	Knockout

VATA	Visceral Adipose Tissue Area
MVP	Million Veteran Program
GLGC	Global Lipids Genetics Consortium
IVW	Inverse Variance-Weighted

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02521-w.

Supplementary Material 1

Supplementary Material 2

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study utilized publicly available data, with informed consent obtained from all participants by the original data collectors. As the analysis was conducted on deidentified data, there were no direct ethical implications. All procedures adhered to the relevant guidelines and regulations to ensure the integrity and ethical compliance of the research.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Center for Reproductive Medicine, Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, China

References
1. Bhardwaj JK, Panchal H, Saraf P. Ameliorating effects of natural antioxidant compounds on female infertility: a review. Reprod Sci. 2021;28:1227–56.
2. Infertility workup for. The women's health specialist: ACOG committee opinion, number 781. Obstet Gynecol. 2019;133:e377–84.
3. Wang G, Yang H, Jiang X, Mao W, Li P, Lin X, et al. Association of serum uric acid with women's ovarian reserve: observational study and Mendelian randomization analyses. Fertil Steril. 2024;122:162–73.
4. Soran H, Schofield JD, Durrington PN. Antioxidant properties of HDL. Front Pharmacol. 2015;6:222.
5. Fujimoto VY, Kane JP, Ishida BY, Bloom MS, Browne RW. High-density lipoprotein metabolism and the human embryo. Hum Reprod Update. 2010;16:20–38.
6. Cai WY, Luo X, Chen E, Lv H, Fu K, Wu XK, et al. Serum lipid levels and treatment outcomes in women undergoing assisted reproduction: a retrospective cohort study. Front Endocrinol (Lausanne). 2021;12:633766.
7. Zhou X, Xu J. Association between serum uric acid-to-high-density lipoprotein cholesterol ratio and insulin resistance in patients with type 2 diabetes mellitus. J Diabetes Investig. 2024;15:113–20.
8. Tan Z, Shen J, Huang Y, Li J, Ding M, Sun A, et al. Decoding connections in the European population: serum uric acid, sex hormone-binding Globulin, total testosterone, estradiol, and female infertility - advanced bidirectional and mediative Mendelian randomization. Front Endocrinol (Lausanne). 2024;15:1398600.
9. Kurtkulagi O, Tel BMA, Kahveci G, Bilgin S, Duman TT, Erturk A, et al. Hashimoto's thyroiditis is associated with elevated serum uric acid to high density lipoprotein-cholesterol ratio. Rom J Intern Med. 2021;59:403–8.
10. Deng F, Jia F, Sun Y, Zhang L, Han J, Li D, et al. Predictive value of the serum uric acid to high-density lipoprotein cholesterol ratio for culprit plaques in patients with acute coronary syndrome. BMC Cardiovasc Disord. 2024;24:155.
11. Yang Y, Zhang J, Jia L, Su J, Ma M, Lin X. Uric acid to high-density lipoprotein cholesterol ratio predicts adverse cardiovascular events in patients with coronary chronic total occlusion. Nutr Metab Cardiovasc Dis. 2023;33:2471–8.
12. Zhou X, Xu J. Association between serum uric acid-to-high-density lipoprotein cholesterol ratio and insulin resistance in an American population: a population-based analysis. J Diabetes Investig. 2024;15:762–71.
13. Xu J, Du X, Zhang S, Zang X, Xiao Z, Su R, et al. Diagnostic value of uric acid to high-density lipoprotein cholesterol ratio in abdominal aortic aneurysms. Ann Med. 2024;56:2357224.
14. Ding L, Guo H, Zhang C, Jiang B, Zhang S, Zhang J, et al. Serum uric acid to high-density lipoprotein cholesterol ratio is a predictor for all-cause and cardiovascular disease mortality in patients with diabetes: evidence from NHANES 2005–2018. Nutr Metab Cardiovasc Dis. 2024;34:2480–8.
15. Chen Z, Cheang I, Qu Q, Zhu X, Fu Y, Gao R, et al. Associations of serum uric acid-to-high density lipoprotein cholesterol ratio with age-related diseases and mortality among older population in the united States. Arch Gerontol Geriatr. 2024;130:105707.
16. Wu MB, Wang R, Zeng QT, Shuai WL, Zhang HC, Dong YF. Association between uric acid to high-density lipoprotein cholesterol ratio and kidney function in patients with primary aldosteronism: a cross-sectional study. J Clin Hypertens (Greenwich). 2025;27:e14960.
17. Li Z, Liu Q, Yao Z. The serum uric acid-to-high-density lipoprotein cholesterol ratio is a predictor for all-cause and cardiovascular disease mortality: a cross-sectional study. Front Endocrinol (Lausanne). 2024;15:1417485.
18. Galveias A, Duarte ESF, Raposo M, Costa MJ, Costa AR, Antunes CM. Trends in land cover and in pollen concentration of Quercus genus in Alentejo, Portugal: effects of climate change and health impacts. Environ Pollut. 2024;362:124996.
19. Hu X, Nie Z, Ou Y, Qian Z, McMillin SE, Aaron HE, et al. Air quality improvement and cognitive function benefit: insight from clean air action in China. Environ Res. 2022;214:114200.
20. Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Willett WC, et al. Predicted lean body mass, fat mass, and all cause and cause specific mortality in men: prospective US cohort study. BMJ. 2018;362:k2575.
21. Seli E, Babayev E, Collins SC, Nemeth G, Horvath TL. Minireview: metabolism of female reproduction: regulatory mechanisms and clinical implications. Mol Endocrinol. 2014;28:790–804.
22. Mu L, Pan J, Yang L, Chen Q, Chen Y, Teng Y, et al. Association between the prevalence of hyperuricemia and reproductive hormones in polycystic ovary syndrome. Reprod Biol Endocrinol. 2018;16:104.
23. Chaudhary K, Malhotra K, Sowers J, Aroor A. Uric acid-key ingredient in the recipe for cardiorenal metabolic syndrome. Cardiorenal Med. 2013;3:208–20.
24. Liu T, Liu D, Song X, Qu J, Zheng X, Li J, et al. Lipid metabolism was associated with oocyte in vitro maturation in women with polycystic ovarian syndrome undergoing unstimulated natural cycle. Front Cell Dev Biol. 2021;9:719173.
25. Li Y, Fan X, Li C, Zhi X, Peng L, Han H, et al. The relationships among hyperuricemia, body mass index and impaired renal function in type 2 diabetic patients. Endocr J. 2018;65:281–90.

26. Didziokaite G, Biliute G, Gudaite J, Kvedariene V. Oxidative stress as a potential underlying cause of minimal and mild endometriosis-related infertility. Int J Mol Sci. 2023;24:3809.

27. Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev. 2015;36:487–525.

28. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.

29. Palomba S, Piltonen TT, Giudice LC. Endometrial function in women with polycystic ovary syndrome: a comprehensive review. Hum Reprod Update. 2021;27:584–618.

30. Arias A, Quiroz A, Santander N, Morselli E, Busso D. Implications of high-density cholesterol metabolism for oocyte biology and female fertility. Front Cell Dev Biol. 2022;10:941539.

31. Semmens J, Rouse I, Beilin LJ, Masarei JR. Relationship of plasma HDL-cholesterol to testosterone, estradiol, and sex-hormone-binding Globulin levels in men and women. Metabolism. 1983;32:428–32.

32. Miettinen HE, Rayburn H, Krieger M. Abnormal lipoprotein metabolism and reversible female infertility in HDL receptor (SR-BI)-deficient mice. J Clin Invest. 2001;108:1717–22.

33. Zhuang J, Wang Y, Wang S, Hu R, Wu Y. Association between visceral adiposity index and infertility in reproductive-aged women in the united States. Sci Rep. 2024;14:14230.

34. Zhu X, Hong X, Wu J, Zhao F, Wang W, Huang L, et al. The association between Circulating lipids and female infertility risk: a univariable and multi-variable Mendelian randomization analysis. Nutrients. 2023;15:3130.

35. Huang X, Hu L, Tao S, Xue T, Hou C, Li J. Relationship between uric acid to high-density cholesterol ratio (UHR) and Circulating alpha-klotho: evidence from NHANES 2007–2016. Lipids Health Dis. 2024;23:244.

Publisher's note