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Research article

# Relationship between maternal serum uric acid in the first trimester and congenital heart diseases in offspring: A prospective cohort study

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ABSTRACT

*Objective:* This study aimed to investigate the relationship between maternal serum uric acid levels in the first trimester and the incidence of congenital heart diseases (CHDs) in offspring.
*Methods:* This prospective cohort study was conducted in the southeast of China and involved 21,425 pregnant women and their offspring in the final analysis between 2019 and 2022. Fasting blood samples from pregnant women participating in the Fujian birth cohort study (11.3 ± 1.40 weeks of gestation) were analyzed for serum uric acid levels. The perinatal outcome was the incidence of CHDs. All fetuses with CHDs were confirmed by echocardiography doctors and pediatric cardiologists. Logistic regression analysis and restricted cubic spline (RCS) modeling were employed to investigate the relationship between serum uric acid level and the incidence of CHDs.
*Results:* We observed that maternal log2-transformed values of serum uric acid were strongly associated with odds of CHDs in offspring (adjusted odds ratio [AOR] 1.589, 95 % CI [1.149, 2.198]). Compared to the lowest quartile, the AORs for maternal uric acid levels in the other quartiles and the corresponding risk of CHDs in offspring were 1.363 (95 % CI [1.036, 1.793]), 1.213 (95 % CI [0.914, 1.610]), and 1.472 (95 % CI [1.112, 1.949]), respectively. Hyperuricemia in the first trimester significantly increased the risk of CHDs in offspring 1.837 (95 % CI [1.073, 3.145]). Furthermore, RCS showed a linear relationship between maternal serum uric acid levels in the first trimester and the incidence of CHDs ($P$ for nonlinearity = 0.71).
*Conclusions:* The results of this study indicated that elevated maternal serum uric acid levels in the first trimester were associated with an increased incidence of CHDs in offspring.

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## 1. Introduction

Congenital heart diseases (CHDs) are the most common congenital anatomical malformation, affecting 5 to 15 infants per 1000 births worldwide, and are the leading cause of perinatal mortality [1–5]. The exact causes of CHDs remain unclear. Previous studies have suggested that maternal disorders related to glucose metabolism, lipid metabolism, and metabolic syndrome can increase the risk of CHDs in offspring [6]. However, only a limited number of studies have focused on exploring the relationship between maternal purine metabolism and CHDs in offspring.

Serum uric acid is the end product of human purine catabolism [7]. It is mainly synthesized via a series of enzymatic reactions involving the breakdown of nucleic acids and other purine compounds resulting from cellular metabolism and from purines present in food [8]. Several epidemiological studies have confirmed that maternal serum uric acid levels during pregnancy are associated with adverse pregnancy outcomes, such as gestational diabetes mellitus (GDM), preeclampsia, and low birth weight infants [9–12]. However, only a limited number of studies have investigated the possible association between maternal serum uric acid levels during pregnancy and the incidence of CHDs in offspring, with results being controversial [13–15]. One study aimed at identifying biomarkers to detect CHDs found that uric acid is a potential marker for CHDs [13]. Another study, which collected maternal serum for metabolomics analysis, found no differential expression of uric acid was found between the CHDs and control groups [14]. However, these studies did not investigate the effect of hyperuricemia on CHDs in offspring, nor did adjust for potential confounding variables in the analysis. At present, no study has examined the linear relationship between maternal serum uric acid levels in the first trimester and the incidence of CHDs in offspring.

With the rapid development of economy, the incidence of hyperuricemia in China is rapidly increasing, particularly in coastal areas [16]. The impact of elevated maternal uric acid levels during pregnancy on the incidence of CHDs in offspring cannot be overlooked. This prospective cohort study, conducted on the southeastern coast of China, aimed to evaluate the relationship between maternal serum uric acid levels in the first trimester and the incidence of CHDs in offspring.

## 2. Method

### 2.1. Data sources and population

The data for this study were obtained from the Fujian Birth Cohort Study (FJBCS), a large and ongoing study aimed at observing the impacts of prenatal exposure to external and internal factors on adverse pregnancy outcomes and fetal birth defects in southeastern

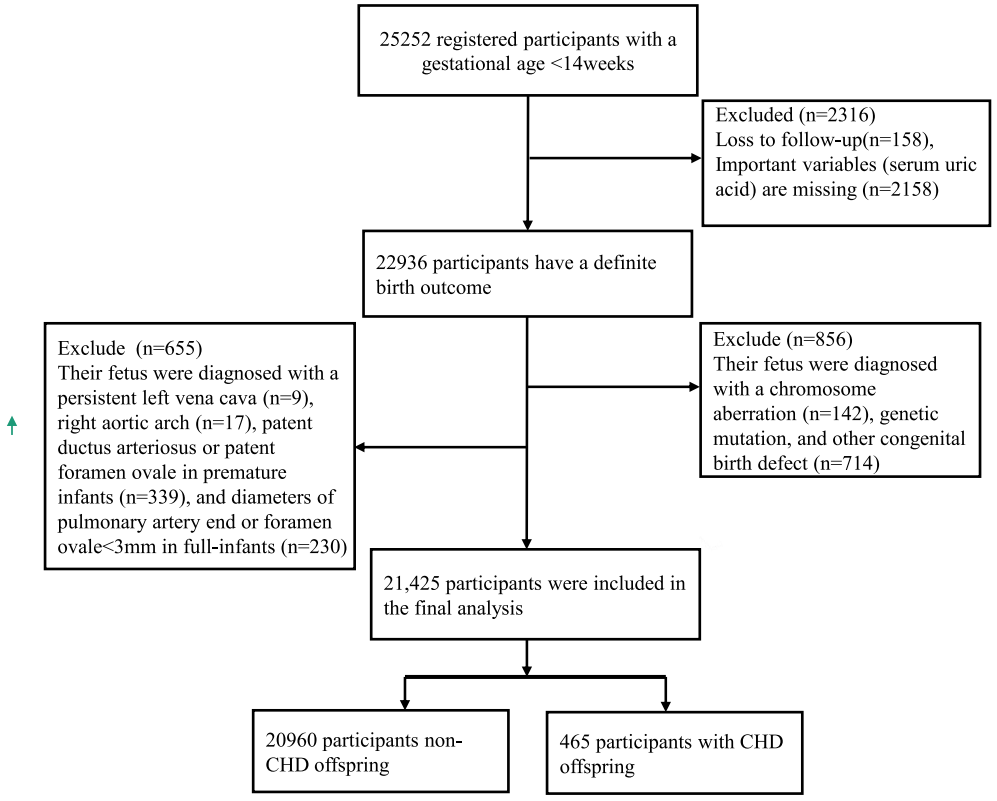


**Fig. 1.** Flow chart of the study cohort and identification of offspring with CHDs.

China. The designs, methods, and inclusion criteria of this birth cohort have been described in previous studies [17,18]. Singleton pregnant women less than 14 weeks gestation and who had their initial prenatal examination at the Obstetrics Clinic of Fujian Maternity and Child Health Hospital were recruited. Gestation week was determined based on the last menstrual period for individuals with irregular menstruation, employing ultrasound for accuracy. A total of 25,252 participants completed a baseline questionnaire and underwent medical examinations during the first trimester between 2019 and 2022. Among these participants, we initially excluded 2316 individuals due to missing serum uric acid results or loss to follow-up. Subsequently, 856 participants were excluded because their offspring had genetic mutations, chromosomal aberrations, or other congenital birth defects. Finally, 655 participants were excluded because their offspring had heart defects that were either spontaneously resolved or clinically nonsignificant. Finally, a total of 21,245 eligible pregnant women who delivered singleton offspring were included in the final analysis. Fig. 1 illustrates the study cohort flowchart and the identification of fetuses with CHDs. This study received approved from the Ethics and Human Trials Committee of Fujian Maternity and Child Health Hospital, and written informed consent was obtained from all participants prior to enrollment.

### 2.2. Serum uric acid measurements

When women first visited the hospital for prenatal examination (at 11.3 ± 1.40 weeks of gestation), fasting blood samples were collected to obtain serum. Serum uric acid level, along with other biochemical indexes such as fasting plasma glucose, blood urea nitrogen (BUN), and creatinine (CREA), were determined at the laboratory of Fujian Maternity and Child Health Hospital using an automatic biochemical analyzer (ABBOTT, ACCELERATOR, a3600, USA). Serum uric acid levels were categorized into four groups based on the quartiles of its distribution: <201.1, 201.1–<230.2, 230.2–<262.9 and ≥ 262.9 μmol/L. Hyperuricemia was defined as a serum uric acid level ≥357 μmol/L, according to the hospital laboratory's reference range or a previous diagnosis of hyperuricemia.

### 2.3. Covariates

During the initial prenatal health examination, all participants underwent face-to-face interviews conducted by trained obstetricians or nurses and completed questionnaires. Blood pressure was measured by healthcare providers. The questionnaire covered sociodemographic characteristics: age (year), body mass index (BMI, in kg/m$^2$), ethnicity (Han and minority in China), residential area (urban and rural), and education level (≤9 years, 9–12 years, >12 years). Obstetric characteristics included assisted reproductive (yes or no) and gravidity (0 or ≥1). Lifestyle factors encompassed smoking (yes or no), alcohol consumption (yes or no) and passive smoking (yes or no), and exposure to environmental pollution (yes or no). BMI was calculated by as weight (kg) divided by height squared (m$^2$). Overweight and obesity were defined as a BMI >24 kg/m$^2$ [19]. Hypertension was diagnosed based on a history of hypertension or a blood pressure≥140/90 mm Hg [20]. GDM was defined as fasting glucose level of >7.0 mmol/L [21].

### 2.4. Outcome variable

The outcome variable was any subtype of CHDs, identified using International Classification of Disease 10th revision (ICD-10) codes (Table 1). The principal diagnosis for combinations of cardiac defects was based on either the most hemodynamically significant structural anomaly or the defect requiring the earliest intervention. Infants during the maternal pregnancy received thorough screening for possible congenital abnormalities using basic ultrasound imaging methods. If CHD was suspected, echocardiography was conducted to comprehensively evaluate the structure and function of the heart, either during the maternal pregnancy or within the first

**Table 1**
All subtypes of CHDs in the study.

| CHD subtypes | Total 465 n (%) | ICD11(LA80-LA90) |
|---|---|---|
| Atrial septal defect | 216(46.5) | LA8E.1 |
| Patent ductus arteriosus (≥37wk) | 116(24.9) | LA8B.4 |
| Ventricular septal defect | 70(15.1) | LA88.4 |
| Endocardial cushion defect | 5(1.1) | LA87.43 |
| Ebstein anomaly | 1(0.2) | LA87.0Y |
| Tetralogy of Fallot | 7(1.5) | LA88.2 |
| Transposition of great arteries | 2(0.4) | LA85.1 |
| Double outlet of right ventricle | 2(0.4) | LA85.2 |
| Hypoplastic left heart syndrome | 1(0.2) | LA89.3 |
| Corrected Transposition of great arteries | 1(0.2) | LA85.00 |
| Tricuspid valve dysplasia | 8(1.7) | LA87.00 |
| Mitral valve dysplasia | 4(0.8) | LA87.10 |
| Complete anomalous pulmonary venous connection | 3(0.6) | LA86.20 |
| Cor triatriatum | 1(0.2) | LA8G.0 |
| Congenital coronary fistula | 3(0.6) | LA8C.2 |
| RVOTO | 11(2.4) | LA88.0 |
| LVOTO | 14(3.0) | LA88.3 |

Abbreviation: CHD, congenital heart disease; RVOTO, right ventricular outflow tract obstruction; LVOTO, left ventricular outflow tract obstruction.

24 h after delivery of the fetuses. The diagnosis of CHD depends on cooperative efforts among specialized professionals, including echocardiography specialists, obstetricians, and pediatric cardiologists. Two trained echocardiography specialists independently reviewed the echocardiographic images of each infant diagnosed with CHD, with mutual blinding to each other's findings. Discrepancies were resolved by additional evaluation from another echocardiography specialist, obstetrician and pediatric cardiologist. Spontaneously resolved defects or clinically nonsignificant forms, such as patent ductus arteriosus (PDA) in preterm infants(<37wk), persistent superior vena cava, right aortic arch, and diameters of pulmonary artery end in full-term infants (≥37wk) <3 mm, were excluded [22–24]. Additionally, the principal diagnosis for combinations of cardiac defects was determined by either the most hemodynamically significant structural anomaly or the defect requiring the earliest intervention [23].

### 2.5. Statistical analyses

Age, BMI, CREA, and BUN were expressed as mean ± standard deviation (SD), while categorical variables were expressed as numbers (percentages). All variables were divided into four groups using the 25th, 50th, and 75th percentiles of uric acid as cutoff points. The chi-square test was used for comparisons among categorical variables, and analysis of variance (ANOVA) was used for continuous variables. Univariate and multivariate logistic regression models were employed to explore the association between quartiles of serum uric acid, log2-transformed values of serum uric acid (normally distributed), hyperuricemia, and the risk of CHDs in offspring. The multivariate logistic regression models were adjusted for age, BMI, ethnicity, residential area, education level, assisted reproductive, gravidity, smoking, alcohol consumption, passive smoking, exposure to environmental pollution, hypertension, GDM, BUN, CREA, and gestation week. Restricted cubic splines (RCS) with four knots were used to explore the dose-response relationship between serum uric acid levels and the incidence of CHDs in offspring.

Additionally, two subgroup analyses were conducted. First, multivariable logistic regression models were used to examine the relationship between maternal serum uric acid in the first trimester and different subtypes of CHDs in offspring, adjusting for all potential confounders. Second, subgroup and interaction analyses were performed for covariates including age, residential area, education level, assisted reproduction, BMI, and hypertension, with adjustments made for potential confounding factors.

All statistical analyses were performed using SPSS (version 26) and R software (version 4.3.3). *P* value less than 0.05 was considered statistically significant.

## 3. Results

### 3.1. Baseline characteristics

Based on the aforementioned exclusion criteria, 3827 participants were excluded, resulting in a final cohort of 21,425 pregnant women were included in the study. Table 2 shows the baseline characteristics of the study population categorized by quartiles of serum uric acid. The mean ± SD maternal serum uric acid levels for the four groups were 177.14 ± 20.20, 215.97 ± 8.27, 245.40 ± 9.30, and

**Table 2**
Baseline characteristics of pregnant women according to quartiles of serum uric acid levels.

| Characteristics | Q1 | Q2 | Q3 | Q4 | *P* |
|---|---|---|---|---|---|
| n | 5364 | 5353 | 5359 | 5349 | – |
| Serum uric acid | 177.14 ± 20.20 | 215.97 ± 8.27 | 245.40(±9.30) | 299.47 ± 35.37 | – |
| Gestation week | 11.05 ± 0.89 | 11.12 ± 0.91 | 11.10 ± 0.90 | 11.17 ± 0.93 | 0.000 |
| Age, year | 32.18 ± 4.03 | 31.94 ± 4.03 | 31.76 ± 4.01 | 31.63 ± 4.14 | 0.000 |
| BMI, kg/m2 | 20.48 ± 2.44 | 20.85(±2.73) | 21.28 ± 2.86 | 22.25 ± 3.48 | 0.000 |
| Ethnicity (Han), n (%) | 5258(98.02) | 5254(98.15) | 5238(97.74) | 5226(97.70) | 0.293 |
| Residence(urban), n (%) | 4881(91.00) | 4887(91.29) | 4872(90.91) | 4809(89.90) | 0.072 |
| Education level, n (%) | | | | | |
| 0–9 years | 1166(21.74) | 1143(21.35) | 1195(22.30) | 1338(25.01) | 0.000 |
| 9–12 years | 3786(70.58) | 3815(71.27) | 3783(70.59) | 3701(69.19) | |
| >12 years | 412(7.68) | 395(7.4) | 381(7.11) | 310(5.80) | |
| Assisted reproductive Technology, n (%) | 346(6.45) | 405(7.57) | 339(6.33) | 557(10.41) | 0.000 |
| Gravidity, (%) | | | | | 0.008 |
| 0 | 1886(35.16) | 1962(36.65) | 2050(38.25) | 1999(37.37) | |
| ≥1 | 3478(64.84) | 3391(63.35) | 3309(61.75) | 3350(62.63) | |
| Smoking, n (%) | 95(1.78) | 104(1.94) | 128(2.39) | 151(2.82) | 0.001 |
| Second smoking, n (%) | 1758(32.77) | 1716(32.06) | 1784(33.29) | 1848(34.55) | 0.046 |
| Alcohol consumption, n (%) | 592(11.04) | 679(12.68) | 640(11.94) | 586(10.96) | 0.015 |
| Exposure to Environmental pollution | 2306(42.99) | 2384(44.54) | 2450(45.72) | 2477(46.31) | 0.003 |
| Hypertension, n (%) | 55(1.03) | 86(1.61) | 88(1.64) | 142(2.65) | 0.000 |
| GDM, n (%) | 12(0.22) | 15(0.28) | 9(0.17) | 29(0.54) | 0.002 |
| CREA, mmol/L | 42.45 ± 6.07 | 43.45 ± 6.28 | 44.25 ± 6.29 | 45.47 ± 7.26 | 0.000 |
| BUN, mmol/L | 2.74 ± 0.62 | 2.85 ± 0.65 | 2.92 ± 0.64 | 3.04 ± 0.71 | 0.000 |

Abbreviation: BMI, body mass index; GDM, gestational diabetes mellitus; CREA, creatinine; BUN, blood urea nitrogen; Data was presented as means ± SD for continuous variable and numbers (percentage) for category variables. The cutoff of serum uric acid levels was <201.1, 201.1–230.2, 230.2–262.9 and ≥ 262.9 μmol/L.

299.47 ± 35.37, respectively. The mean ± SD age for the four groups was 32.18 ± 4.03, 31.94 ± 4.03, 31.76 ± 4.01, and 31.63 ± 4.14, respectively. Across increasing uric acid quartiles, there was a progressive rise in the prevalence of hypertension and GDM (all $P < 0.05$). Furthermore, significant differences were observed in BMI, CREA, BUN, and gestation week among the quartile groups. Elevated serum uric acid levels were associated with higher BMI, CREA, and BUN levels (all $P < 0.05$).

### 3.2. Relationship between maternal serum uric acid in the first trimester and CHDs in offspring

As depicted in Table 3, compared to the lowest quartile of maternal uric acid levels in the first trimester, both the second quartile (adjusted risk ratio (AOR) 1.363, 95 % CI [1.036, 1.793]) and the highest quartile (AOR 1.472, 95 % CI [1.112, 1.949]) showed increased incidence of CHDs in offspring after adjusting for potential confounders. However, this association was not significant in the third quartile (AOR 1.213, 95 % CI [0.914, 1.610]). Maternal log2-transformed values of serum uric acid were positively correlated with CHDs risk in offspring (AOR 1.589, 95 % CI [1.149, 2.198]). Compared to normal pregnant women, those with hyperuricemia in the first trimester experienced an 83.7 % increase in the risk of CHDs (AOR 1.837, 95 % CI: 1.073, 3.145). Additionally, RCS analysis indicated a significant linear relationship between maternal serum uric acid and the risk of CHDs in offspring ($P$ for nonlinearity = 0.73) (Fig. 2).

### 3.3. Subgroup analysis

We further exposure the relationship between maternal serum uric acid in the first trimester and the risk of different subtypes of CHDs in offspring. As presented in Fig. 3, compared to the lowest quartile of UA, the second quartile (AOR 1.692, 95 % CI [1.061, 2.699]) and the highest quartile (AOR 1.997, 95 % CI [1.252, 3.187]) were associated with an increased the risk of atrial septal defect (ASD) in offspring. No significant associations were observed between serum uric acid levels in the first trimester and the risk of PDA, ventricular septal defect (VSD), or other subtypes of CHDs in offspring. Furthermore, the association between maternal serum uric acid in the first trimester and CHDs in offspring was more obvious in participants aged >30 (AOR 1.611, 95 % CI [1.072, 2.422]), residing in urban areas(AOR 1.628, 95 % CI [1.157, 2.292]), with 9–12 years of education(AOR 1.819, 95 % CI [1.224, 2.703]), not using assisted reproduction(AOR 1.547, 95 % CI [1.095, 2.186]), having a BMI<24 kg/m$^2$(AOR 1.617, 95 % CI [1.116, 2.342]), and without hypertension(AOR 1.541, 95 % CI [1.110, 2.138]) compared to their respective reference groups (Fig. 4).

## 4. Discussion

In this prospective cohort study conducted on the southeast coast of China, we observed a significant positive correlation between maternal serum uric acid levels in the first trimester and the risk of CHDs in offspring. This relationship persisted even after adjusting for potential confounders, including age, BMI, ethnicity, residential, education level, assisted reproductive technology, gravidity, smoking, alcohol consumption, passive smoking, exposure to environmental pollution, hypertension, GDM, BUN, CREA, and gestation week. Maternal hyperuricemia was also identified as an independent risk factor for CHDs in offspring. The study population resides on the southeast coast of China, where long-term consumption of seafood, such as fish and shrimp, is closely associated with the incidence of hyperuricemia [25]. Exploring the relationship between serum uric acid levels and CHDs in offspring is of great clinical significance. This exploration could potentially inform dietary recommendations for pregnant women and contribute to reducing the incidence of

**Table 3**
The relationship between maternal serum uric acid level in the first trimester and the risk of CHDs in offspring.

| Trend across UA quartiles | CHD/ participants | Unadjusted OR (95%CI) P | Model 1 AOR (95%CI) P | Model 2 AOR (95%CI) P | Model3 AOR (95%CI) P |
|---|---|---|---|---|---|
| Q1 | 92/5364 | 1reference | 1reference | 1reference | 1 reference |
| Q2 | 124/5353 | 1.359(1.035,1.784) 0.027 | 1.352(1,029,1.776) 0.030 | 1.347(1.025,1.769) 0.032 | **1.363(1.036,1.793) 0.027** |
| Q3 | 111/5359 | 1.212(0.917,1.602) 0.177 | 1.193(0.902,1.578) 0.216 | 1.191(0.900,1.576) 0.221 | 1.213(0.914,1.610)0.182 |
| Q4 | 138/5349 | 1.158(1.162,1.981) 0.002 | 1.449(1.106,1.897) 0.007 | 1.429(1.091,1.873)0.01 | **1.472(1.112,1.949) 0.007** |
| P for trend | – | 0.017 | 0.041 | 0.053 | **0.040** |
| log2UA | – | 1.640(1.208,2.226) 0.001 | 1.546(1.136,2.104) 0.006 | 1.379(1.006,1.888) 0.046 | **1.589(1.149,2.198) 0.005** |
| Hyperuricemia | | | | | |
| Yes | 15/356 | 2.016(1.092,3.409) 0.009 | 1.858(1.095,3.152) 0.022 | 1.832(1.078,3.113) 0.025 | **1.837(1.073,3.145) 0.027** |
| No | 450/21069 | 1 reference | 1 reference | 1 reference | 1 reference |

Abbreviation: CHDs, congenital heart diseases; OR, odds ratio; AOR, adjusted odds ratio. The cutoff of serum uric acid levels was <201.1, 201.1–230.2, 230.2–262.9 and ≥ 262.9 μmol/L.
Model 1: adjusted for age, BMI, ethnicity, residential, education level, assisted reproductive technology, gravidity, smoking, alcohol consumption, passive smoking, and exposure to environmental pollution.
Model 2: adjusted for model 1 + hypertension and gestational diabetes mellitus.
Model 3: adjusted for model 2+ blood urea nitrogen, creatinine, and gestation week.

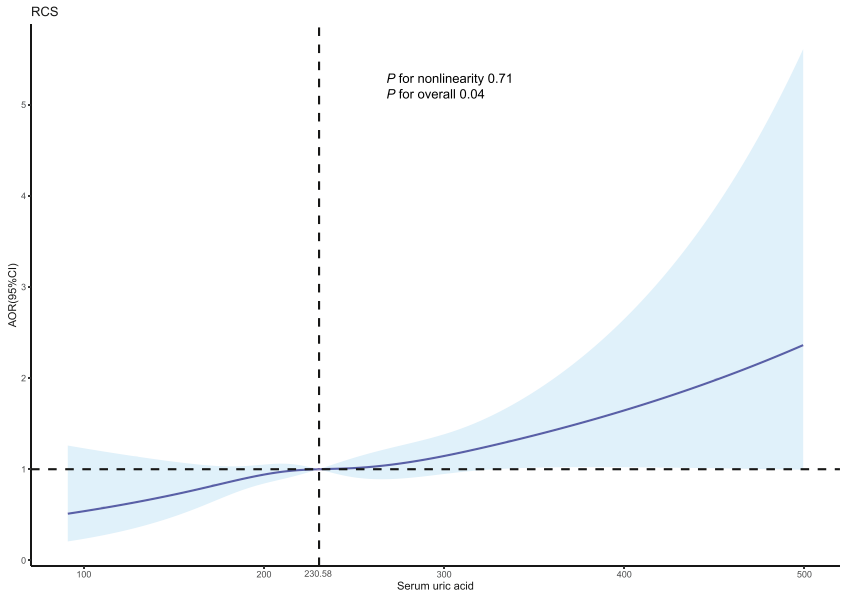


**Fig. 2.** Dose-response relationship between maternal serum uric acid level in the first trimester and the risk of CHDs in offspring.
The dose-response relationships were evaluated in the restricted cubic spline analysis based on the logistic regression model. The red line indicates the AOR value, while the blue area denotes the 95 % confidence interval. Abbreviation: RCS, restricted cubic spline; AOR, adjusted odds ratio; AOR has adjusted for age, BMI, ethnicity, residential, education level, assisted reproductive technology, gravidity, smoking, alcohol consumption, passive smoking, exposure to environmental pollution, hypertension, gestational diabetes mellitus, blood urea nitrogen, creatinine, and gestation week.

CHDs.

The mechanisms underlying the association between maternal serum uric acid in the first trimester and CHDs in offspring remain unclear. Uric acid, a physiologically abundant compound during embryonic development, is known to facilitate stable myocardial differentiation crucial for mesodermal development [7]. Firstly, elevated uric acid levels can activate the NLRP3 inflammasome, promoting the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-18 (IL-18), and tumor necrosis factor-α (TNF-α) [26]. These cytokines can directly damage endothelial cells and induce inflammation. Nitric oxide (NO) is essential for vascular endothelial cell function and survival [27]. Impaired endothelial function, characterized by reduced NO production [28,29], exacerbates endothelial dysfunction and impacts cardiovascular development and function. Secondly, maternal metabolic disorders, including hypertension, hyperglycemia, and hyperinsulinemia, are linked to increased CHDs risk in offspring [6]. Elevated serum uric acid levels correlate with these metabolic disturbances [30,31], suggesting uric acid may influence fetal cardiovascular development through metabolic pathways. Furthermore, high uric acid levels may activate pathological pathways like IκBα/NF-κB and MAPK signaling [32], pivotal in regulating cell death and tissue damage [33,34]. These mechanisms potentially elucidate the association between maternal uric acid levels and CHDs in offspring. However, further basic and clinical trials are imperative to validate these hypotheses and explore specific mechanisms comprehensively in future research.

After identifying uric acid as a potential biomarker for CHDs in amniotic fluid, Yahong Li et al. measured serum uric acid levels in the second trimester among mothers with CHDs-affected and unaffected fetuses. However, they did not observe any significant differences in serum uric acid levels between the two groups [14]. This discrepancy may stem primarily from their measurement timing in the second trimester, whereas the critical cardiac development occurs in the first trimester [35]. Additionally, their smaller sample size (29 in the case group and 58 in the control group) could have impacted their findings. In contrast, a study that involving 5390 pregnant women aimed at predicting CHDs prevalence based on clinical laboratory data found results consistent with ours. They reported a 27 % higher risk of CHDs among mothers with elevated uric acid levels (>261 μmol/L) compared to those with levels ≤261 μmol/L [15]. Fang et al. also noted a significant difference in serum uric acid levels between 17 pregnant women with fetal CHDs and 63 pregnant women with non-CHDs fetuses in their analysis of peripheral serum metabolites [13]. However, they did not explore the dose-response relationship between serum uric acid levels and CHDs incidence. Moreover, their case-control study design introduced selection bias and did not adjust for important confounding factors such as hypertension and GDM.

In this study, ASD, PDA, and VSD are the top three CHDs, accounting for 86 % of all cases of CHDs. This prevalence ranking is consistent with global findings reported in previous studies [36]. The exact mechanism underlying this pattern remains unclear, although several factors are likely contributors. The widespread adoption and extensive use of echocardiography have significantly increased CHD detection rates, enabling the identification of minor conditions such as small ASDs, PDAs, and VSDs [37]. Furthermore, accumulating evidence indicates that parental lifestyle factors during pregnancy, such as smoking, alcohol consumption, maternal pre-existing conditions, and other environmental teratogenic influences, may elevate the risk of CHDs [38]. These environmental factors primarily affect heart development by predisposing to minor malformations rather than severe defects like transposition of the great arteries or tetralogy of Fallot. The pathogenesis of these severe defects likely involves complex interactions and additional

| Subgroup | Case | AOR(95%CI) | *P* Value | *P* for trend |
|---|---|---|---|---|
| ASD(216) | | | | |
| Q1 | 36 | reference | | 0.032 |
| Q2 | 57 | 1.692(1.061,2.699) | 0.027 | |
| Q3 | 53 | 1.506(0.934,2.428) | 0.093 | |
| Q4 | 70 | 1.997(1.252,3.187) | 0.004 | |
| log2UA | | 2.219(1.320,3.729) | 0.003 | |
| PDA(>3mm)(116) | | | | |
| Q1 | 26 | reference | | 0.542 |
| Q2 | 27 | 1.052(0.611,1.811) | 0.855 | |
| Q3 | 27 | 1.073(0.620,1.857) | 0.802 | |
| Q4 | 36 | 1.416(0.830,2.417) | 0.202 | |
| log2UA | | 1.600(0.840,3.048) | 0.153 | |
| VSD(70) | | | | |
| Q1 | 14 | reference | | 0.788 |
| Q2 | 20 | 1.382(0.694,2.749) | 0.357 | |
| Q3 | 16 | 1.069(0.516,2.214) | 0.858 | |
| Q4 | 20 | 1.226(0.597,2.518) | 0.579 | |
| log2UA | | 1.190(0.526,2.695) | 0.677 | |
| Others(63) | | | | |
| Q1 | 16 | reference | | 0.544 |
| Q2 | 20 | 1.278(0.658,2.480) | 0.469 | |
| Q3 | 15 | 0.949(0.463,1.944) | 0.885 | |
| Q4 | 12 | 0.748(0.341,1.644) | 0.470 | |
| log2UA | | 0.778(0.333,1.818) | 0.562 | |

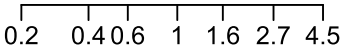


**Fig. 3.** The relationship between maternal serum uric acid in the first trimester and the risk of different subtypes of CHDs in offspring.
Abbreviation: ASD, atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect; Others, the total number of the CHDs of other subtypes except for ASD, PDA, and VSD in Table 1. UA, uric acid; AOR, adjusted odds ratio; AOR adjusted for age, BMI, ethnicity, residential, education level, assisted reproductive technology, gravidity, smoking, alcohol consumption, passive smoking, exposure to environmental pollution, hypertension, gestational diabetes mellitus, blood urea nitrogen, creatinine, and gestation week.

predisposing conditions, contributing to their relatively lower incidence [39].

In the subgroup analysis, serum uric acid was identified as a risk factor for ASD in offspring. However, no association was found between maternal serum uric acid levels and the risk of VSD, PDA (diameter $>$ 3 mm), or other types of CHDs. Specifically, among the group with other types of CHDs, which primarily include severe case as detailed in Table 1, a stronger relationship might have been anticipated but was not observed due to the limited sample size of only 63 medical records for these conditions, potentially lacking sufficient statistical power. Further clinical and foundational research is crucial to elucidate the specific underlying mechanism. To explore the data and assess the robustness of our results, we conducted an additional subgroup analysis. This analysis revealed no significant interactions between maternal uric acid levels and the stratified variables, suggesting that additional factors did not influence the association between maternal uric acid levels and CHDs in offspring. The biological mechanisms behind the differential associations observed within these specific subgroups remain unclear. Notably, no significant association between maternal uric acid levels and CHDs in offspring was found among mothers younger than 30 years old in this study. This absence of association could be attributed to higher antioxidant levels in younger mothers, potentially mitigating the oxidative stress typically associated with elevated uric acid levels. Among participants with a BMI greater than 24, maternal uric acid levels did not influence the risk of CHDs in offspring. Previous studies have indicated a positive correlation between maternal BMI and the risk of CHDs in offspring [40], suggesting that obesity reflects combined effects of metabolic status, nutritional intake, and inflammatory status [41] that could directly impact fetal cardiovascular development, potentially altering the relationship between maternal uric acid levels and CHDs in offspring. Furthermore, no significant association was observed among participants with hypertension. The small sample size in this subgroup

| Stratification covariates | Incidents/participants | AOR(95%CI) | *P* | *P* for trend |
|---|---|---|---|---|
| Age(years) | | | | 0.376 |
| ≤30 | 175/8110 | 1.529(0.895,2.613) | 0.120 | |
| >30 | 290/13315 | 1.611(1.072,2.422) | 0.022 | |
| Residential area | | | | 0.583 |
| Urban | 421/19449 | 1.628(1.157,2.292) | 0.005 | |
| Rural | 44/1976 | 1.260(0.443,3.583) | 0.665 | |
| Education levels(years) | | | | 0.550 |
| ≤9 | 116/4842 | 1.184(0.635,2.207) | 0.595 | |
| 9<-12 | 321/15085 | 1.819(1.224,2.703) | 0.003 | |
| ≥12 | 28/1498 | 1.125(0.296,4.275) | 0.863 | |
| Assisted reproductive | | | | 0.678 |
| Yes | 52/1747 | 2.112(0.804,5.546) | 0.129 | |
| No | 413/19678 | 1.547(1.095,2.186) | 0.013 | |
| BMI(kg/m$^2$) | | | | 0.724 |
| <24 | 360/17745 | 1.617(1.116,2.342) | 0.011 | |
| ≥24 | 105/3680 | 1.671(0.850,3.285) | 0.136 | |
| Hypertension | | | | 0.056 |
| Yes | 11/371 | 6.633(0.568,77.521) | 0.131 | |
| No | 454/21054 | 1.541(1.110,2.138) | 0.010 | |

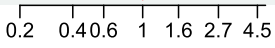


**Fig. 4.** Subgroup analysis of the association between maternal serum uric acid levels in the first trimester and CHDs in offspring across various population stratifications.
Each stratification adjusted for all the factors (age, BMI, ethnicity, residential, education level, assisted reproductive technology, gravidity, smoking, alcohol consumption, passive smoking, exposure to environmental pollution, hypertension, gestational diabetes mellitus, blood urea nitrogen, creatinine, and gestation week) except the stratification factor itself. Abbreviation: AOR, adjusted odd ratio; CI, confidence interval; BMI, body mass index.

may have limited statistical power [42], potentially hindering the detection of associations between maternal uric acid levels and CHDs in offspring. It is important to note that these findings are based on single-center studies, which may limit their generalizability.

## 5. Strengths ang limits

Our study has several strengths. Firstly, this large prospective birth cohort study, involving 21,425 pregnant women, enhances the credibility of the results due to its robust design and substantial sample size. Secondly, we measured fasting serum uric acid levels in the first trimester, which covers the key window of fetal heart development. Thirdly, this study was the first to explore the association between hyperuricemia, different serum uric acid levels and the incidence of CHDs in offspring on the basis of cohort study design. However, our study also has some limitations. Firstly, although we have adjusted for potential confounding factors as much as possible in the multivariate analysis, we cannot rule out the presence of other confounding factors, such as dietary nutrition and physical activities, which could bias the results due to limited information. Future studies should collect and adjust for these confounding factors to comprehensively understand the relationship between maternal serum uric acid levels and the risk of CHDs in offspring. Secondly, although we excluded cardiac defects with self-healing tendencies and no obvious clinical manifestations [22,43–45] the incidence of congenital heart disease remained at 2.17 %, which is slightly higher than the previously reported incidence (0.5%–1.5 %) [1–4]. This could be attributed to the fact that this was a single-center study carried out in one of the largest hospitals equipped with both obstetric diagnosis and treatment centers as well as pediatric cardiovascular diagnosis and treatment centers in southeastern China. Thirdly, this study did not account for the number of multiple births or analyze their influence on CHDs. Future research should explore the association between maternal multiple pregnancies and the risk of CHDs in offspring. Finally, the single-center design may limit the generalizability of our findings to other populations.

## 6. Conclusions

Overall, this study identified a significant association between elevated maternal serum uric acid levels in the first trimester and an increased risk of CHDs in offspring. This finding suggest that we should pay attention to maternal serum uric acid levels and give timely early treatment and recommendations to reduce the incidence of CHDs.

## Data availability statement

The raw data used in this study are available from the corresponding author upon reasonable request.

## Ethics statement

The study was approved by the Medical Ethics Committee of Fujian Maternal and Child Health Hospital (approval number: 2017 KR-030). All the pregnant women participating in this study have signed the informed consent form.

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## CRediT authorship contribution statement

**Minli Zhao:** Writing – original draft, Conceptualization. **Xinrui Wang:** Visualization. **Danwei Zhang:** Data curation. **Haibo Li:** Data curation. **Yibing Zhu:** Validation, Conceptualization. **Hua Cao:** Supervision, Funding acquisition, Conceptualization.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Hua Cao reports financial support was provided by Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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