# Association between maternal serum lipid profiles in early pregnancy and the risk of congenital heart disease in offspring: a prospective cohort study

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# Abstract

**Objective:** This study aims to investigate the association of maternal serum lipid profiles in early pregnancy and the risk of congenital heart disease (CHD) in offspring.

**Methods:** This study was based on the Fujian Birth Cohort Study (FJBCS) which was a prospective ongoing study in China. We recruited pregnant women at ≤14 weeks of gestation between 2019 and 2022, and all participants in this study filled out the questionnaire on periconceptional exposure. Simultaneously, we collected participants' fasting blood samples to measure their lipid profiles by automatic biochemical analyzer. The outcome was defined as offspring with or without CHD. In a multivariable logistic regression model, risk estimates were calculated for associations between maternal lipid profiles and CHD in offspring. Restricted cubic splines were used to estimate the nonlinear relationship between lipid profiles levels and CHD.

**Results:** A total of 21425 pregnant women with an average gestational age of 11.3 (± 1.40) weeks were included in the analysis. The higher triglyceride (TG) (AOR 1.201, 95%CI [1.036,1.394]), low-density lipoprotein (LDL) (AOR 1.216, 95% CI [1.048,1.410]), apolipoprotein B (Apo B) (AOR 2.107, 95% CI [1.179,3.763]) levels were correlated with increased odds of CHD in offspring. The restricted cubic spline suggested a nonlinear relationship between total cholesterol (TC) levels and the risk of CHD in offspring (P=0.0048).

**Conclusions**: Elevated maternal serum lipid profiles levels are associated with an increased risk of CHD in offspring. Additionally, there is a non-linear relationship between TC levels and the risk of CHD in offspring.


# 1. INTRODUCTION

Congenital heart disease (CHD) is one of the most prevalent congenital malformations, impacting approximately 5 to 15 per 1000 live births worldwide.[1–4] Although the mortality of CHD has decreased for the advances in diagnostic and therapeutic techniques, its impact on the quality of life can extend to adulthood or even longer.[5, 6] Therefore, there is an urgent need to prevent CHD by investigating modifiable risk factors and proposing practical preventive strategies.

The embryo is susceptible to the influence of maternal metabolic factors during pregnancy. Maternal lipid profile, as one of these crucial prenatal metabolic factors, plays a significant role in the occurrence and progression of congenital malformations[7] such as neural tube defects,[8] autism spectrum disorder,[9] as well as CHD.[10] It also contributes to adverse pregnancy outcomes, including gestational diabetes mellitus, hypertension, and premature births.[11] However, limited and controversial studies have investigated the association between lipid profile levels during pregnancy and the risk of CHD in offspring. A previous study reported that elevated lipid profile levels, determined at around 16 months after the index pregnancy, were associated with an increased risk of CHD in offspring.[12] However, the

critical period for cardiac tissue differentiation and development occurs in early pregnancy.[13] A cohort study from the Netherlands found that both low and high TG levels in early pregnancy were risk factors for cardiovascular anomalies in offspring.[7] However, this relationship disappeared after adjusting for confounding factors. Another retrospective case-control study from China summarized that levels of TG, Apo A, and Apo B in early pregnancy were significantly higher in the CHD group compared to the control group.[10] However, the researchers did not explore the non-linear relationship between lipid profile and the risk of CHD in offspring.

This study, based on a large birth cohort in southeast China, aims to investigate the association between serum lipid profiles levels in early pregnancy and the risk of CHD in offspring, including exploring the nonlinear relationship between them.

# 2. METHODS

## 2.1. Study design and population

This prospective population-based cohort study was conducted based on the Fujian Birth Cohort Study (FJBCS), which was commenced in 2019 at Fujian Maternal and Child Health Hospital in Fujian, China for exploring the relationship between perinatal exposure and adverse pregnancy outcomes. The method and design details of the FJBCS study have been previously described.[14] Briefly, pregnant women of gestational age ≤ 14 weeks were invited to complete the registration during their first prenatal visit at our hospital. Pregnant women diagnosed with multiple pregnancies, severe cardiovascular disease, cerebrovascular disease, liver or kidney failure, or family history of CHD were not enrolled in the study. This study recruited a total of 25,252 participants who completed early pregnancy examinations between January 2019 and February 2022. All participants received face-to-face interviews conducted by trained nurses and filled out a questionnaire. Simultaneously, we collected their fasting blood samples. Among these participants, we first excluded those who were still pregnant at the end of follow-up, lost to follow-up. We further excluded pregnant women whose offspring had genetic mutations, chromosomal aberrations, or other congenital birth defects. Finally, we excluded pregnant women whose offspring were diagnosed with clinically nonsignificant forms or spontaneously resolved defects, including persistent left superior vena cava(PLSVC), right aortic arch(RAA), patent foramen ovale or patent ductus arteriosus in premature infants(< 37wk), or the diameters of patent foramen or pulmonary artery end < 3mm in full-term infants (≥ 37wk).[10, 15–17]The final analysis included 21,245 singleton pregnant women and their fetuses. Figure 1 showed the participant flowchart. All procedures of this study were approved by the ethics committee of Fujian Provincial Maternal and Child Health Hospital (Approval number: 2017KR-030) and written informed consent was signed by every participant. We also confirmed that all research was performed in accordance with Declaration of Helsinki.

## 2.2. Serum lipid profiles

Serum lipid profiles were determined using an automatic biochemical analyzer at our hospital's laboratory, which includes TC, TG, HDL, LDL, Apo A, Apo B. The process of biochemical analyses was performed in the following steps: 1. Peripheral blood was collected during the first registration at ≤ 14 weeks' gestation. 2. The whole blood was collected into tubes with anticoagulant (EDTA or citrate) and transferred to the laboratory within 10 minutes. After incubating at room temperature for 20 minutes, the tubes were centrifuged at 3,000 rpm for 20 minutes. The supernatant was carefully collected as a plasma sample. 3. Biochemical indexes were analyzed using corresponding kits on an automatic biochemical analyzer (ABBOTT, ACCELERATOR, a3600, USA).

# 2.3. Outcome

The outcome was defined as offspring with or without CHD. Each case of CHD was diagnosed according to the standardized criteria outlined in the internationally recognized framework known as the International Classification of Diseases version 10 (ICD-10), and subtypes were classified by the codes Q20–Q26. Cases of CHD include live births, stillbirths, and aborted fetuses diagnosed with CHD. Fetuses underwent comprehensive screening for potential congenital defects using basic ultrasound imaging techniques. Echocardiography was employed to meticulously screen fetuses that showed suspicion of having a congenital heart defect. The confirmation of all CHD cases was achieved through a collective effort involving highly skilled professionals, including ultrasound doctors, obstetricians, pediatric cardiac surgeons, and pediatric physicians. For combined cardiac defects, the primary diagnosis was determined based on either the defect requiring the earliest intervention or the most hemodynamically significant structural anomaly.

# 2.4. Confounders

In this study, the confounders are defined and categorized as follows: 1. Sociodemographic factors: maternal age, ethnicity(Han and ethnic minorities), residence(urban and rural), educational level(12, 12–16 and > 16years), and monthly income in CNY(4500, 4500–9000 and > 9000 yuan); 2. Obstetric characteristics: gravidity(0, 1, ≥ 2), assisted reproduction(yes or no); 3.Health behaviors: fever(yes or no), diabetes mellitus(yes or no), hypertension(yes or no), medication history (any medication other than non-nutritive substances)(yea or no); 4. Environmental factors: exposure to toxic substances (gasoline, pesticides, noise, radiation, heavy metals) (yes or no) and exposure to air pollution(yes or no); 5. Lifestyle characteristics: smoking(yes or no), passive smoking(yes or no), drinking(yes or no); 6. Nutritional supplements: vitamin supplementation(yes or no), folic acid supplementation (yes or no), DHA supplementation(yes or no), cod-liver oil supplementation(yes or no), and calcium supplementation(yes or no). The exposure time of the above confounders was defined as “6 months before conception to early pregnancy” and collected from self-reported questionnaires. Body mass index (BMI) was calculated by dividing weight (in kg) by the square of height (in m2). The height and weight of pregnant women were measured during registration in early pregnancy, and the pre-pregnancy/early pregnancy BMI was obtained since weight gain is limited during this stage.[18] The BMI category was determined based on the Chinese adult BMI classification standard as follows: underweight (< 18.5 kg/m2), normal weight (18.5-<24 kg/m2), overweight (24-<28 kg/m2), and obesity (≥ 28 kg/m2).[19]

## 2.5. Statistical analysis

For baseline characteristics, continuous variables are expressed as mean ± standard deviation, while categorical variables are presented as number (percentages). Descriptive analysis for continuous variables was conducted using Student's t-tests, and chi-square tests or Fisher's exact tests were performed for categorical variables. Variables with statistically significant differences were used as potential confounders to be adjusted in the multivariate analysis later. Multivariable logistic regression models were used to calculate adjusted odds ratios (AORs) and their 95% confidence intervals (CIs) while controlling for potential confounders. These potential confounders were determined based on the analysis results mentioned above. The specific steps are as follows: (1) Model 1, adjusted for gravidity, assisted reproduction, medication history, exposure to air pollution, and passive smoking. (2) Model 2, adjusted for variables in Model 1 as well as fasting blood glucose and BMI. The concentrations of lipid profiles were divided into quartiles, with the 25th to 75th percentile serving as the reference group. We used restricted cubic spline curves based on logistic regression models with four knots at the 5th, 35th, 65th, and 95th percentiles to assess the nonlinear relationship between levels of lipid profiles and the odds ratios of CHD. In the subgroup analysis, the relationship between blood lipid levels and the risk of CHD in offspring were stratified by different BMI stratifications with the same analysis methods. Additionally, we conducted a sensitivity analysis with the identical analytical approach, excluding pregnant women with lipid profile levels below the 2.5th percentile and above the 97.5th percentile, and re-evaluated the association with the risk of CHD in offspring. All statistical analyses were performed using SPSS software version 27 and R software version 4.2.3. A p-value of less than 0.05 was considered statistically significant.

# 3. RESULTS

## 3.1. Population characteristics

From January 2019 to February 2022, a total of 21,245 pregnant women were included in our final study, with a mean (± SD) gestational age of 11.3 (± 1.40) weeks. Among them, 465 women delivered CHD fetuses and 20,960 women delivered non-CHD fetuses. The baseline characteristics of pregnant women are presented in Table 1. Compared with other participants in the study, pregnant women with higher BMI levels($P < 0.001$), primiparity($P = 0.003$), assisted reproduction($P = 0.016$), a history of medication use($P = 0.043$), exposure to air pollution($P = 0.002$), and passive smoking($P = 0.018$) were more likely to give birth to CHD fetuses.

Table 1
Baseline characteristics of mothers with or without CHD fetuses in early pregnancy

| | Total | CHD | No CHD | *P* |
|---|---|---|---|---|
| Characteristic | (n = 21425) | (n = 465) | (n = 20960) | |
| Year† | 31.88(± 4.06) | 31.94(± 4.097) | 31.88(± 4.060) | 0.620 |
| BMI (kg/m2) ‡ | | | | 0.000 |
| <18.5 | 3074(14.3) | 57(12.30) | 3017(14.10) | |
| 18.5-<24 | 14671(68.5) | 303(65.20) | 14368(67.10) | |
| 24-<28 | 2940(13.7) | 73(15.70) | 2867(13.40) | |
| ≥ 28 | 740(3.5) | 32(6.90) | 708(3.30) | |
| Ethnicity (han)‡ | 20976(97.9) | 9(1.9) | 440(2.1) | 0.807 |
| Residence(urban)‡ | 19449(90.8) | 421(90.5) | 19028(90.8) | 0.857 |
| Education level‡ | | | | 0.382 |
| <12years | 4842(22.6) | 116(24.9) | 4728(22.6) | |
| 12-16years | 15085(70.4) | 321(69.0) | 14764(70.4) | |
| >16years | 1498(7.0) | 28(6.0) | 1470(7.0) | |
| Monthly income, CNY‡ | | | | 0.143 |
| <4500 | 9118(42.6) | 215(46.2) | 8903(42.6) | |
| 4500–9000 | 8735(40.8) | 187(40.2) | 8548(39.9) | |
| >9000 | 3513(16.4) | 63(13.5) | 3450(16.5) | |
| missing | 59(0.3) | 0 | 59(0.3) | |
| Gravidity‡ | | | | 0.003 |
| 0 | 7897(36.9) | 179(38.5) | 7718(36.8) | |
| 1 | 1476(6.9) | 49(10.5) | 1427(6.8) | |
| ≥ 2 | 12052(56.3) | 237(51.0) | 11815(56.4) | |
| Assisted reproduction‡ | 1747(8.2) | 52(11.2) | 1695(8.1) | 0.016 |

Abbreviation: CHD, congenital heart disease; BMI, body mass index.

† Mean (SD), Student's t -test; ‡ n (%), chi-square test

| | Total | CHD | No CHD | *P* |
|---|---|---|---|---|
| fever‡ | 658(3.1) | 11(2.4) | 647(3.1) | 0.373 |
| Diabetes mellitus‡ | 460(2.1) | 97(20.9) | 3802(18.1) | 0.133 |
| Hypertension‡ | 3899(18.2) | 14(3.0) | 446(2.1) | 0.194 |
| Medication history‡ | 10387(48.5) | 247(53.1) | 10140(48.4) | 0.043 |
| Exposure to air pollution‡ | 9617(44.9) | 242(52.0) | 9375(44.7) | 0.002 |
| Smoking‡ | 478(2.2) | 6(1.3) | 472(2.3) | 0.165 |
| Passive smoking‡ | 7106(33.2) | 178(38.3) | 6928(33.1) | 0.018 |
| Drinking‡ | 2497(11.7) | 45(9.7) | 2452(11.7) | 0.179 |
| Vitamin supplementation‡ | 11229(52.4) | 243(52.3) | 10986(52.4) | 0.947 |
| Folic acid supplementation‡ | 13106(61.2) | 280(60.2) | 12826(61.2) | 0.669 |
| DHA supplementation‡ | 1679(7.8) | 41(8.8) | 1638(7.8) | 0.426 |
| Cod-liver oil supplementation‡ | 246(1.1) | 6(1.3) | 240(1.1) | 0.771 |
| Calcium supplementation‡ | 2499(11.7) | 58(12.5) | 2441(11.6) | 0.583 |
| Abbreviation: CHD, congenital heart disease; BMI, body mass index. | | | | |
| † Mean (SD), Student's t -test; ‡ n (%), chi-square test | | | | |

# 3.2. Serum lipid profiles

The serum lipid profiles of pregnant women with or without CHD fetuses are shown in Table 2. Maternal levels of TG(P = 0.002), LDL(P = 0.001), and Apo B(P = 0.001) were higher among mothers delivering CHD fetuses compared to those delivering non-CHD fetuses. However, maternal levels of HDL(P = 0.001) and Apo A (P = 0.016) were lower in pregnant women delivering CHD fetuses compared to pregnant women delivering non-CHD fetuses.

Table 2
Blood biochemical indexes of mothers with or without CHD fetuses in early pregnancy

| Characteristics | CHD (Mean ± SD) | non-CHD (Mean ± SD) | *P* |
|---|---|---|---|
| n | 465 | 20960 | - |
| Blood glucose(mmol/L) | 4.79 ± 0.70 | 4.75 ± 0.42 | 0.203 |
| TC (mmol/L) | 4.70 ± 0.79 | 4.63 ± 0.74 | 0.090 |
| TG (mmol/L) | 1.45 ± 0.57 | 1.37 ± 0.53 | 0.002 |
| HDL (mmol/L) | 1.63 ± 0.29 | 1.68 ± 0.30 | 0.001 |
| LDL (mmol/L) | 2.50 ± 0.65 | 2.40 ± 0.40 | 0.001 |
| Apo A(g/L) | 1.46 ± 0.28 | 1.49 ± 0.27 | 0.016 |
| Apo B(g/L) | 0.75 ± 0.17 | 0.73 ± 0.16 | 0.001 |
| ALT(U/L) | 17.36 ± 13.90 | 17.05 ± 16.39 | 0.681 |
| AST(U/L) | 17.65 ± 6.25 | 17.62 ± 8.21 | 0.994 |
| FT4(ng/dl) | 1.33 ± 0.22 | 1.34 ± 0.27 | 0.252 |
| TSH (uIU/ml) | 1.11 ± 0.94 | 1.13 ± 1.05 | 0.566 |

Abbreviation: SD, standard deviation; CHD, congenital heart disease; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo A, apolipoprotein A; Apo B, apolipoprotein B; ALT, aminotransferase; AST, aspartate aminotransferase; FT4, free thyroxine; TSH, Thyroid-stimulating hormone.

## 3.3. Relationships between maternal serum lipid profiles and CHD in offspring

As shown in Table 3, compared to the reference group (25th-75th percentile, 4.14–5.08), pregnant women with maternal TC levels in early pregnancy above the 75th percentile (AOR 1.452, 95% CI: [1.166, 1.808]) significantly increased the risk of CHD in offspring after adjusting for confounders. In addition, pregnant women with TG levels above the 75th percentile (AOR 1.249, 95% CI: [1.003, 1.555]), LDL levels above the 75th percentile (AOR 1.420, 95% CI: [1.144, 1.764]), and Apo B levels above the 75th percentile (AOR 1.430, 95% CI: [1.139, 1.795]) had a 24.9%, 42.0%, and 43.0% higher risk of CHD in offspring, respectively, when compared to the reference group (25th-75th percentile, TG: 1.03–1.59, LDL: 1.99–2.75, Apo B: 0.6–0.8). As continuous variables, elevated TG (AOR 1.201, 95% CI [1.036, 1.394]), LDL (AOR 1.216, 95% CI [1.048, 1.410]) and Apo B (AOR 2.107, 95% CI [1.179, 3.763]) levels were positively correlated with the risk of CHD in offspring after adjusting for the identified confounding factors. In addition, there was a U-shaped nonlinear relationship between maternal TC levels in early pregnancy and the risk of CHD in offspring (P for nonlinear 0.0048), as illustrated in Fig. 2.

Table 3
Associations between maternal lipid profiles as continuous and categorical variables in early pregnancy and risk of CHD in offspring

| | unadjusted | model1 | Model2 |
|---|---|---|---|
| | OR [95% CI] *P* | AOR [95% CI] *P* | AOR [95% CI] *P* |
| **TC** | | | |
| ≤ 25th | 1.264(1.008,1.585)0.043 | 1.273(1.015,1.597)0.037 | 1.297(1.033,1.627)0.025 |
| 25th-75th | reference | reference | reference |
| >75th | 1.488(1.197,1.851)0.000 | 1.486(1.194,1.849)0.000 | 1.452(1.166,1.808)0.001 |
| Continuous variables | 1.120(0.982,1.265)0.068 | 1.116(0.987,1.261)0.080 | 1.090(0.963,1.233)0.173 |
| **TG** | | | |
| ≤ 25th | 0.899(0.709,1.140)0.378 | 0.896(0.706,1.137)0.366 | 0.912(0.718,1.158)0.449 |
| 25th-75th | reference | reference | reference |
| >75th | 1.330(1.075,1.645)0.009 | 1.333(1.075,1.653)0.009 | 1.249(1.003,1.555)0.047 |
| Continuous variables | 1.270(1.108,1.455)0.001 | 1.265(1.099,1.455)0.001 | 1.201(1.036,1.394)0.016 |
| **HDL** | | | |
| ≤ 25th | 1.293(1.049,1.595)0.016 | 1.263(1.024,1.558)0.029 | 1.203(0.972,1.487)0.089 |
| 25th-75th | reference | reference | reference |
| >75th | 0.824(0.644,1.053)0.122 | 0.832(0.651,1.065)0.144 | 0.852(0.666,1.090)0.203 |
| Continuous variables | 0.580(0.425,0.791)0.001 | 0.608(0.445,0.630)0.002 | 0.672(0.490,0.920)0.013 |
| **LDL** | | | |
| ≤ 25th | 1.069(0.845,1.351)0.579 | 1.080(0.854,1.365)0.519 | 1.111(0.878,1.406)0.382 |
| 25th-75th | reference | reference | reference |
| >75th | 1.519(1.228,1.880)0.000 | 1.489(1.202,1.844)0.000 | 1.420(1.144,1.764)0.001 |
| Continuous variables | 1.296(1.124,1.485)0.000 | 1.274(1.103,1.472)0.001 | 1.216(1.048,1.410)0.010 |

Abbreviation: CHD, congenital heart disease; AOR, adjusted odds ratio; CI, confidence interval; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo A, apolipoprotein A; Apo B, apolipoprotein B; Cut-off value: TC, 25th: 4.14, 75th: 5.08; TG, 25th: 1.03, 75th: 1.59; HDL, 25th: 1.47, 75th: 1.87; LDL, 25th: 1.99, 75th: 2.75; Apo A, 25th: 1.29, 75th: 1.64; Apo B, 25th: 0.6, 75th: 0.8. Model 1: adjusted for gravidity, assisted reproduction, medication history, exposure to air pollution, passive smoking; Model 2: adjusted for model 1 + blood glucose + BMI.

| | unadjusted | model1 | Model2 |
|---|---|---|---|
| **Apo A** | | | |
| ≤ 25th | 1.245(1.008,1.536)0.042 | 1.211(0.980,1.496)0.076 | 1.171(0.946,1.448)0.147 |
| 25th-75th | reference | reference | reference |
| >75th | 0.777(0.606,0.995)0.046 | 0.823(0.641,1.056)0.126 | 0.824(0.642,1.058)0.129 |
| Continuous variables | 0.652(0.461,0.924)0.016 | 0.742(0.520,1.058)0.099 | 0.776(0.545,1.106)0.160 |
| **Apo B** | | | |
| ≤ 25th | 0.977(0.783,1.219)0.836 | 0.980(0.785,1.223)0.857 | 1.011(1.139,1.795)0.921 |
| 25th-75th | reference | reference | reference |
| >75th | 1.502(1.201,1.879)0.000 | 1.504(1.201,1.883)0.000 | 1.430(1.139,1.795)0.002 |
| Continuous variables | 2.553(1.460,4.463)0.001 | 2.575(1.464,4.528)0.001 | 2.107(1.179,3.763)0.012 |

Abbreviation: CHD, congenital heart disease; AOR, adjusted odds ratio; CI, confidence interval; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo A, apolipoprotein A; Apo B, apolipoprotein B; Cut-off value: TC, 25th: 4.14, 75th: 5.08; TG, 25th: 1.03, 75th: 1.59; HDL, 25th: 1.47, 75th: 1.87; LDL, 25th: 1.99, 75th: 2.75; Apo A, 25th: 1.29, 75th: 1.64; Apo B, 25th: 0.6, 75th: 0.8. Model 1: adjusted for gravidity, assisted reproduction, medication history, exposure to air pollution, passive smoking; Model 2: adjusted for model 1 + blood glucose + BMI.

## 3.4. Subgroup analysis

Figure 3 illustrated the relationship between maternal lipid profiles in early pregnancy and CHD in offspring, stratified by different BMI levels. After adjusting for potential confounders, we observed that a maternal lipid profiles with high TC levels (AOR 1.31, 95% CI [1.03, 1.68]), LDL levels (AOR 1.41, 95% CI [1.06, 1.88]), and Apo B levels (AOR 3.68, 95% CI [1.18, 11.53]) in early pregnancy was associated with an increased risk of CHD in offspring only among overweight/obese pregnant women (BMI ≥ 24 kg/m²).

## 3.5. Sensitivity analysis

After excluding pregnant women with lipid profiles levels below the 2.5th percentile and above the 97.5th percentile, the results regarding the relationship between TG, HDL, LDL, Apo B, and CHD in offspring remained robust, as shown in Table S1. The ORs and 95% CIs were as follows: TG (AOR 1.332, 95% CI [1.051, 1.688]), HDL (AOR 0.688, 95% CI [0.475, 0.996]), LDL (AOR 1.326, 95% CI [1.098, 1.601]), and Apo B (AOR 2.109, 95% CI [1.017, 4.371]).

# 4. DISSCUSSION

In this prospective cohort study from China, we observed a strong association between elevate serum lipid profiles levels in early pregnancy and increased risk of CHD in offspring after adjusting for potential confounding factors, except for HDL. When exploring the nonlinear relationship, we discovered a visually distinct U-shaped nonlinear relationship between TC and the risk of CHD in offspring. The results of subgroup analyses revealed that the risk of CHD increased with elevated TC, LDL, and Apo B levels in overweight/obese pregnant women, while this trend was not observed in underweight and normal-weight mothers. Furthermore, HDL was found to significantly related to lower risk of CHD only in normal-weight pregnant women.

Maternal lipid metabolism during normal pregnancy can be divided into anabolic and catabolic phases.[20] The first trimester represents a significant anabolic phase.[21] During this period, lipid profiles levels continue to increase to meet the growing physiological requirements of the fetus.[7, 22, 23] However, it has been demonstrated that higher concentrations of lipid profiles can increase the risk of birth defects in offspring.[7]

TC and TG were the two most common lipids in the human body. H.P.M. Smedts et al. conducted a case-control study to recruit mothers of children with CHD (n = 261) and children without CHD (n = 325). The subjects' lipid profiles levels were measured approximately 16 months after giving birth. Their study revealed that elevated TC levels significantly increased the risk of CHD in offspring.[12] Another nested case-control study from China did not find any association between TC levels in early pregnancy and the risk of CHD in offspring.[10] Consistent with the results of the above studies, we found that each unit increase in TC levels did not significantly increase the risk of CHD in offspring. However, being the first study to investigate the non-linear relationship between cholesterol levels in early pregnancy and the risk of CHD in offspring, we discovered that both excessively high and excessively low TC levels increased the risk of CHD in offspring. Smedts et al. and Cao Let et al. found that maternal TG levels were positively correlated with the risk of CHD in offspring.[10, 12] However, Jan MR et al. from Pakistan did not find that maternal TG levels were associated with the risk of CHD in offspring.[24] In this study, we observed a significant linear relationship between TG levels and the risk of CHD in offspring, which is closely associated with the risk of CHD. The variations in research design and differences in the timing of lipid profiles assessments may account for the disparities observed in the aforementioned results. Fasting lipid profiles and non-fasting lipid profiles may also exert a slight effect on the results.[25] There is no normal lipid profiles reference range for pregnant women, although both mothers and infants are susceptible to adverse lipid environments during pregnancy.[23] When TC and TG were used as categorical variables, the cut-off points for TC were 4.14 mmol/L and 5.08 mmol/L, respectively. The cut-off points for TG were 1.03 mmol/L and 1.59 mmol/L, respectively. Compared to the reference group, maternal TC levels lower than or equal to 4.14 mmol/L and higher than 5.08 mmol/L, as well as TG levels higher than 1.59 mmol/L, could significantly increase the risk of CHD in offspring. However, the reference ranges of TC and TG in Chinese normal adults were below 5.2 mmol / L and below 1.7 mmol / L, respectively.[26] Our results provided evidence for the development of serum lipid profiles levels in early pregnancy in southeastern China.

Consistent with previous reports,[12, 27]this study demonstrates that increased LDL levels during pregnancy are associated with an increased risk of having a child with CHD. LDL can enter the blood vessel wall, leading to vascular obstruction and increasing the risk of cardiovascular disease.[28] In addition, high levels of maternal LDL can enter the fetal circulatory system through endothelial cells of the placental barrier,[29] which may potentially affecting the fetal heart development. Apo A and Apo B play important roles in lipid metabolism, cholesterol transport, absorption, and metabolism. Several studies have shown the relationship between Apo A and Apo B levels during pregnancy and pregnancy outcomes.[30–32]Smedts et al. and Cao L et al. both found that maternal Apo B levels in early pregnancy were the best predictor of CHD in offspring, but this relationship weakened after adjusting for confounding factors in Cao L et al.'s study.[10, 12]In our study, maternal Apo B levels was strongly positively correlated with the risk of CHD in offspring, but Apo A levels has no relationship with CHD. The reasons for the difference in results may be the same as those mentioned above, but the specific mechanism needs to be further verified through molecular experiments.

To the best of our knowledge, no association has been reported between altered lipid profiles stratified by different maternal BMI levels and the risk of CHD. In subgroup analysis, the results revealed that in overweight/obese mothers, women with higher TC, LDL, and Apo B levels were associated with an increased risk of CHD. It has been confirmed that overweight/obese women are more likely to experience pathological manifestations of dyslipidemia during pregnancy.[33, 34] In addition, maternal overweight/obese during pre/early pregnancy is associated with an elevated risk of CHD in offspring.[35, 36] So we can speculate that elevated blood lipid levels may serve as a potential mechanism through which maternal overweight/obese increases the risk of CHD in offspring. However, the specific causal relationship of this association needs to be further explored through more studies.

Although the mechanism of the adverse effects of elevated maternal lipid profiles levels on embryonic heart development is not completely clear, it is biologically reasonable. Hyperlipidemia has been shown to increase oxidative stress levels in the body.[37] Increased oxidative stress might lead to CHD, through ROS production, which affects inter- and intracellular signaling pathways.[38] According to the genetic background of the embryo, exposure to maternal lipid profiles alteration may affect the neural crest, which is involved in embryonic heart development.[39] There is a close relationship between lipid profiles and fatty acids. Abnormal serum lipid profiles levels, such as hyperlipidemia, can lead to disorders in fatty acid metabolism. Fatty acids are involved in embryonic development and play a crucial role in intracellular signaling pathways, contributing to the synthesis of receptor ligands and cell membranes.[40] However, a study has found that high levels of palmitic acid suppress embryonic GATA-binding protein 4 signaling and cause CHD.[41] Thus, during the critical period of cardiac development, an increase in maternal serum lipid profiles levels may result in alterations in cardiac development by impacting mechanisms such as oxidative stress and gene expression.

The major strengths of this study were as follows: First, when compared with previous studies,[7, 10, 12] this study was conducted as a prospective cohort study with a substantial sample size, which greatly

enhances the reliability of the obtained results. Second, six important blood lipid profiles were measured and analyzed during early pregnancy, which was a critical period for cardiac development.[13] Third, this study was the first to demonstrate a nonlinear relationship between TC levels in early pregnancy and the risk of CHD in offspring. However, this study also had several limitations. First, despite adjusting for the majority of possible confounding factors, there were still potential residual confounding factors. Second, the majority of factors measured in this study were dichotomous variables rather than continuous variables, which had the potential to mask their true associations with CHD. Third, it was important to note that this study is a single-center cohort study conducted in China, which might restrict the generalizability of our findings to other ethnic groups.

# 5. CONCLUSION

In this study, we discovered that higher TG, LDL, and Apo B levels in early pregnancy were associated with an increased risk of CHD in offspring. Conversely, HDL showed a negative correlation with the risk of CHD in offspring. It is important to consider the potential nonlinear relationship when exploring the influence of lipid profiles on CHD risk. Additionally, both serum lipid profiles and BMI levels in early pregnancy should be taken into account when assessing their roles in offspring CHD risk. The result of this study indicates that early detection and intervention for maternal serum lipid profiles disorder may help to reduce the risk of CHD.

# Declarations

### CONTRIBUTION TO AUTHORSHIP

C.H. and Z.Y.B. conceptualized the study. L. H. B, S.B and W. Z. Q collected the data. Z. M. L conducted the data analysis and drafted the original version of the manuscript. C. H, Z. Y. B, W. X. R, and Z. D. W revised and edited the manuscript, focusing on important content. All authors are responsible for ensuring the accuracy and have approved the final versions of this manuscript.

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### DISCLOSURE OF INTERESTS

None

### DATA AVAILABILITY

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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# Figures

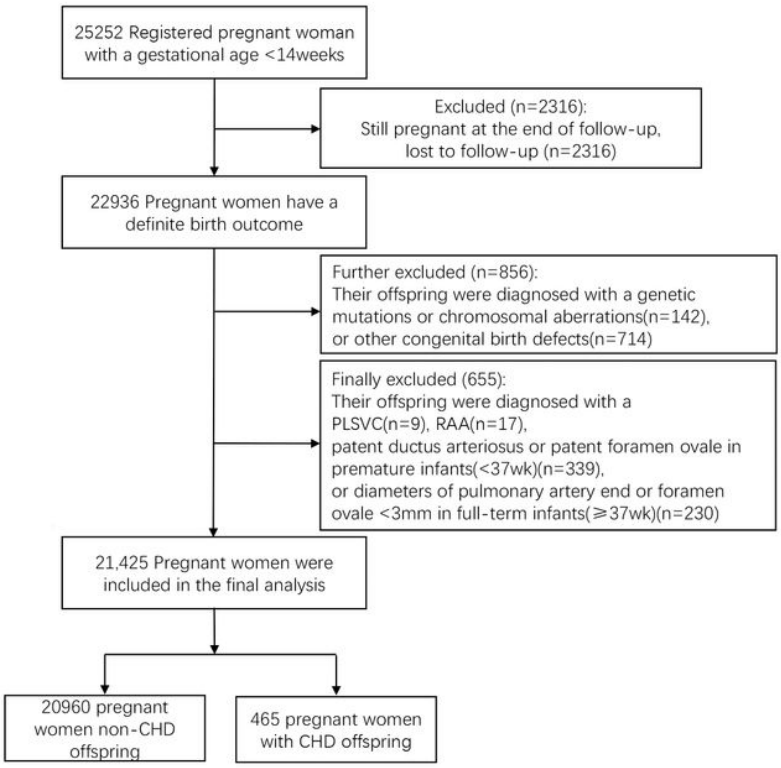
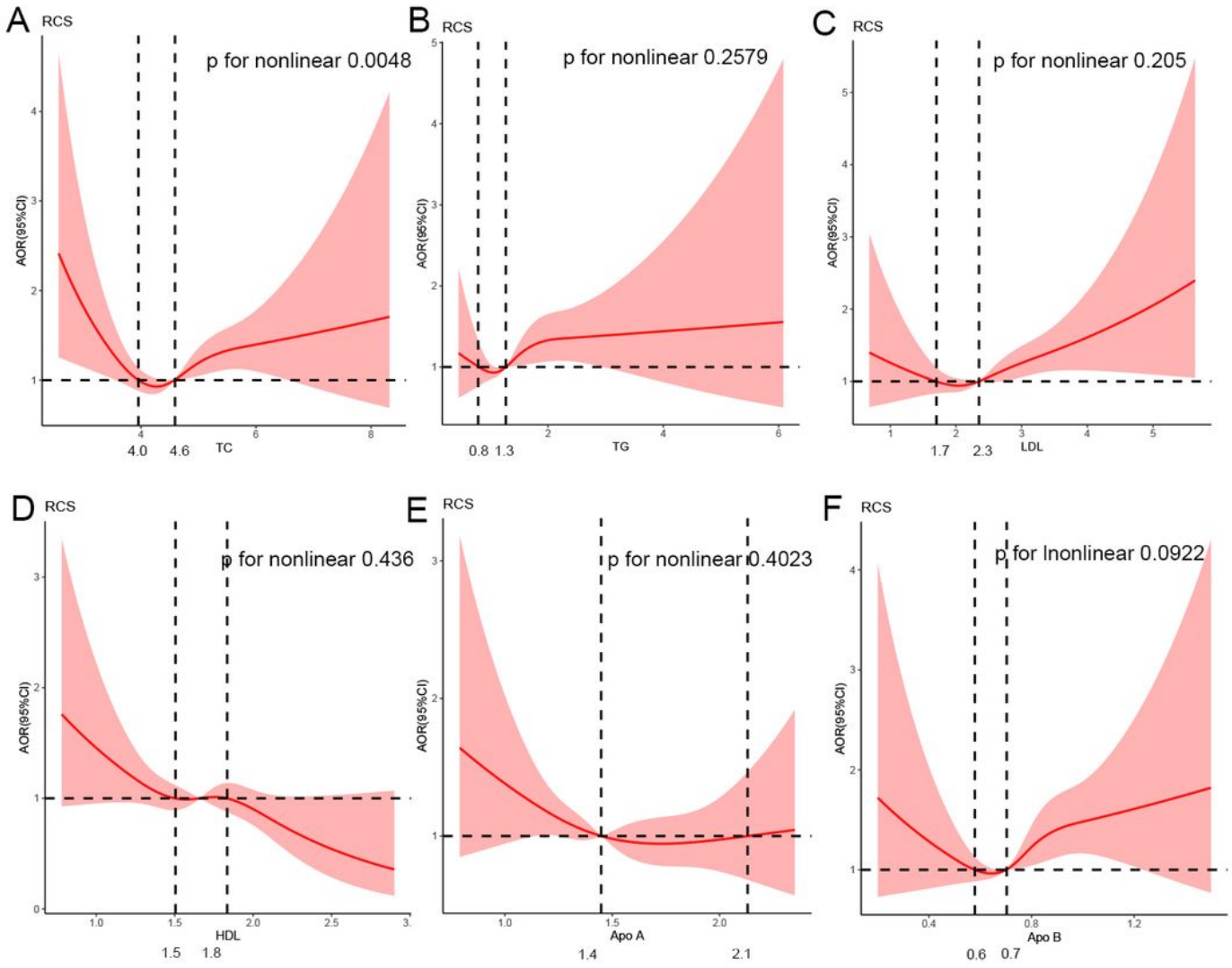



**Figure 1**

**Flow chart of the study cohort and identification of fetus with congenital heart disease.**

Abbreviations: PLSVC, persistent left superior vena cava; RAA, right aortic arch; CHD, congenital heart disease.




## Figure 2

### Dose-response relationship between maternal serum lipid profiles in early pregnancy and risk of CHD in offspring

Abbreviation: TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo A, apolipoprotein A; Apo B, apolipoprotein B; RCS, restricted cubic spline; AOR, adjusted

odds ratio; AOR is adjusted for gravidity, assisted reproduction, medication history, exposure to air pollution, passive smoking, blood glucose, BMI.

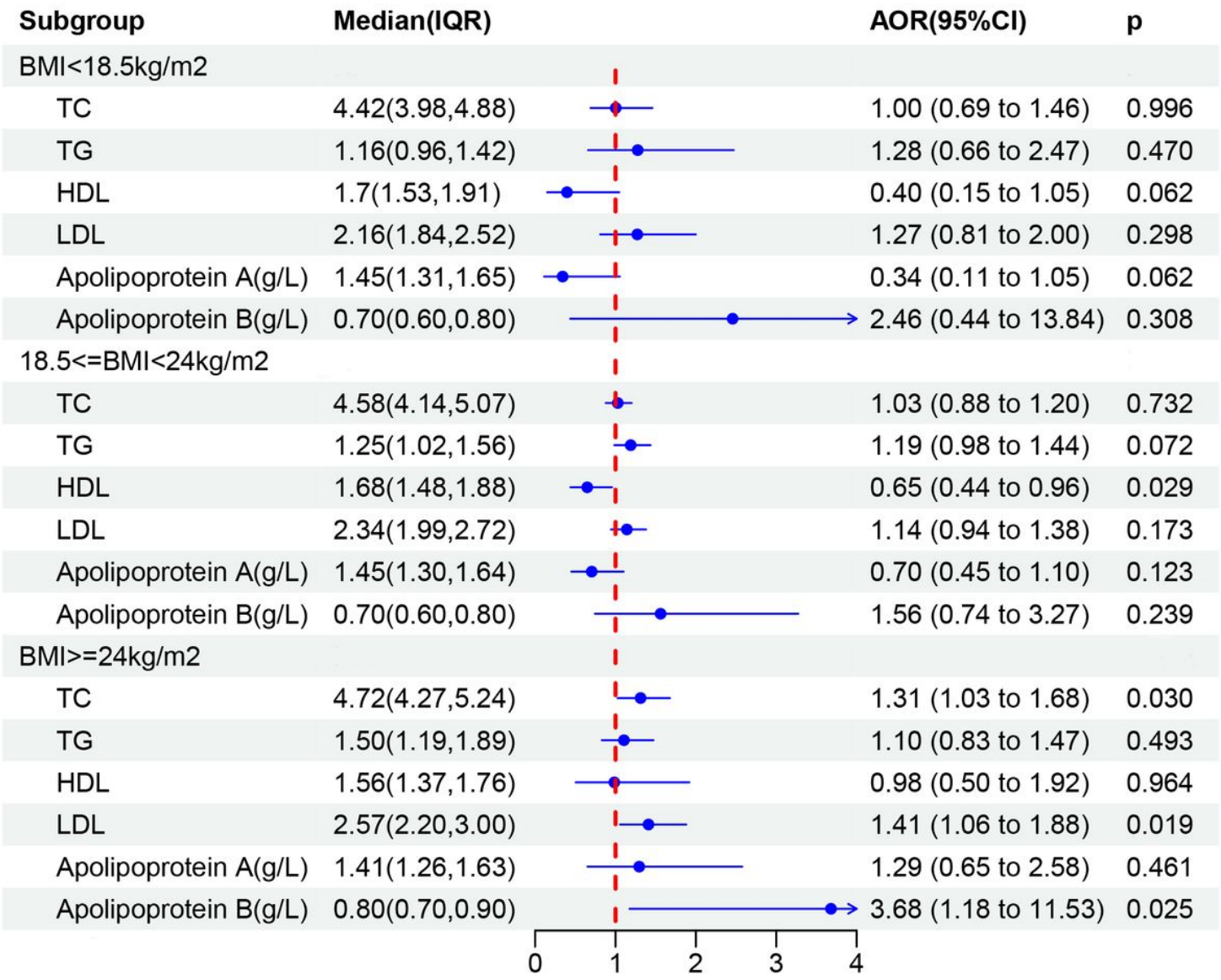



**Figure 3**

**Forest plots showing the relationship between maternal serum lipid profiles levels in early pregnancy and CHD in offspring stratified by different BMI levels.**

Abbreviation: TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI : body mass index; IQR: Inter-quartile range; AOR  Adjusted odds ratio; CI: confidence interval. AOR adjusted for adjusted for gravidity, assisted reproduction, medication history, exposure to air pollution, passive smoking, fasting blood glucose, BMI.

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