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Trimester-specific reference intervals for blood lipid levels and their associations with adverse pregnancy outcomes in Southeast China

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Abstract

Background Trimester-specific reference intervals (TSRIs) for maternal lipid profiles should be determined, and the impact of dyslipidemia on adverse pregnancy outcomes (APOs) should be estimated.

Methods Data from 25,081 pregnant women in a large Southeast Chinese cohort were collected. Serial lipid profiling was performed throughout gestation, with measurements obtained during the first, second, and third trimesters, as well as within 24 h of delivery. The truncated maximum likelihood (TML) method, the Hoffman method, and inverse modelling were employed to establish TSRIs for lipids, with TML as the primary method. The associations of dyslipidemia with APOs were investigated by logistic regressions within the setting of TSRIs for various lipids.

Results The TSRIs established by the TML method were as follows: 3.36–6.06, 4.19–7.89, 4.60–8.97, and 4.41–8.79 mmol/L for total cholesterol; 0.66–2.32, 1.11–3.75, 1.49–4.77, and 1.61–6.14 mmol/L for triglycerides; 1.42–3.61, 1.94–5.13, 1.95–5.39, and 1.86–5.50 mmol/L for low-density lipoprotein cholesterol; 1.11–2.31, 1.30–2.75, 1.24–2.59, and 1.20–2.65 mmol/L for high-density lipoprotein cholesterol; 1.89–4.20, 2.59–5.85, 2.87–6.17, and 2.88–6.78 mmol/L for non-high-density lipoprotein cholesterol; 1.04–1.96, 1.25–2.41, 1.23–2.46, and 1.25–2.47 g/L for apolipoprotein A1; 0.43–0.82, 0.63–1.17, 0.65–1.55, and 0.79–1.77 g/L for apolipoprotein B; and 0.27–0.79, 0.35–0.94, 0.39–1.11, and 0.40–1.15 for the apolipoprotein B and apolipoprotein A1 ratio from the first trimester to the delivery period, respectively. The results of the Hoffman and inverse modelling methods closely aligned with those of the TML method. In pregnant women, lipid levels that deviate above or below the established TSRIs are significantly associated with the occurrence of APOs.

Conclusion TSRIs are recommended for the identification and management of dyslipidemia during pregnancy. Inappropriate maternal blood lipid levels are associated with an increased risk of APOs.

Keywords Blood lipid levels, Dyslipidemia, Reference intervals, Adverse pregnancy outcomes

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Introduction

Dyslipidemia during pregnancy poses immediate and long-term health risks to both mothers and offspring [1]. Abnormal lipid levels are closely associated with the occurrence of adverse pregnancy outcomes (APOs), such as macrosomia, preterm birth, gestational diabetes mellitus (GDM), and preeclampsia (PE) [2, 3]. Currently, trimester-specific reference intervals (TSRIs) for blood lipid profiles remain unstandardized, leading to the lack of unified clinical guidelines for their management. Consequently, this poses significant challenges to clinical practice. Although interventions such as those involving omega-3 fatty acids and statins are extensively utilized in cholesterol management, their safety and efficacy in pregnant individuals require further investigation and validation [4]. Therefore, the precise identification and management of dyslipidemia during pregnancy is essential to guarantee the health of pregnant women and their offspring.

Lipid metabolism changes during pregnancy play critical roles in fetal growth and maternal physiological adaptations. Elevated maternal levels of high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and total cholesterol (TC) have been linked to an increased risk of gestational diabetes mellitus (GDM), preeclampsia (PE), macrosomia, and large-for-gestational-age (LGA) infants, whereas a negative correlation has been found with small-for-gestational-age (SGA) infants [2, 3, 5]. In contrast, reduced levels of TG and low-density lipoprotein cholesterol (LDL-C) have been associated with a lower risk of GDM, LGA infants, and preterm birth. However, no significant associations were found between decreased HDL-C levels and the development of GDM or PE [6, 7]. Moreover, lower maternal HDL-C levels during the third trimester are significantly associated with an increased likelihood of delivering infants with macrosomia and LGA [8]. Previous research has indicated that irregularities in lipid metabolism may lead to fetal endothelial dysfunction and atherosclerosis, which can significantly increase the risk of cardiovascular disease in adulthood [9]. Elevated levels of maternal TG are also linked to a greater probability of cardiovascular disease in both mothers and fetuses [10]. Thus, monitoring maternal TC, LDL-C, and non-high-density lipoprotein cholesterol (non-HDL-C) levels is an effective way to assess the risk of developing hypertension or cardiovascular disease [11]. In addition, higher TG levels, as well as the apolipoprotein B and apolipoprotein A1 (Apo-B/Apo-A1) ratio, increase the risk of PE and preterm birth. Conversely, higher Apo-A1 levels are inversely linked to the risk of uterine atony and postpartum hemorrhage [12–14].

The physiological elevation of lipid levels during pregnancy may be misclassified as hyperlipidemic if assessed using the reference values recommended by the *Chinese Guidelines for Lipid Management (2023)*, potentially leading to unnecessary anxiety and stress in pregnant women [15]. This discrepancy arises because the guideline-recommended reference values fall within the range of TSRIs established in previous studies [16–18]. While numerous studies have focused on establishing TSRIs for the first, second, or third trimesters, the literature has fragmented and incomplete coverage of the entire pregnancy period. For example, Zheng et al. [16] applied the Hoffmann method to define TSRIs for the entire pregnancy except for the delivery period, whereas Wang et al. [18] focused on the first and third trimesters. Notably, no studies to date have established lipid reference intervals specifically for the delivery period. This omission is concerning, as lipid levels during delivery may differ significantly from those in the third trimester owing to dramatic fluctuations in hormone levels, circulatory system adjustments, and changes in energy metabolism. Therefore, TSRIs should account for the dynamic physiological changes in lipid levels throughout pregnancy to ensure accurate clinical assessment. Furthermore, previous research has been limited in scope, often focusing narrowly on the four major maternal blood lipids (TC, TG, HDL-C, LDL-C) and employing relatively simple methodologies such as the Hoffmann and percentile methods. Research on other maternal lipids, such as Apo-A1, Apo-B, non-HDL-C, and the Apo-B/Apo-A1 ratio, remains limited. These biomarkers are also essential for assessing the metabolic health of pregnant and postpartum women and providing precise guidance for clinical management.

This study aimed to utilize the truncated maximum likelihood (TML) method, reverse modelling, and Hoffmann approach to establish TSRIs for blood lipid levels throughout pregnancy in a large cohort in southeastern China. Furthermore, this study also aimed to evaluate the relationship between dyslipidemia, as defined by these TSRIs, and APOs.

Methods

Data source

The Fujian Birth Cohort Study (FJBCS) is a large prospective cohort study conducted in Southeast China that focuses on investigating the effects of exposure on maternal and infant health. Researchers have previously described the conceptual design and methodology of the FJBCS study [19]. In summary, pregnant women were registered and received early care at the prenatal clinic of Fujian Provincial Maternal and Child Health Hospital. During their first visit, eligible participants who were older than 18 years and less than 14 weeks pregnant were invited to participate. The data were collected from singleton pregnant women with normal pre-pregnancy

lipid levels from January 2019 to June 2023 and covered the early pregnancy period (9–12 weeks) and different trimesters. The exclusion criteria were as follows: (1) multiple births; (2) major somatic or psychiatric diseases, including but not limited to malignancies or hepatic diseases; (3) previously diagnosed hypertension, diabetes, and chronic thyroid, kidney and cardiovascular conditions; (4) lipid-lowering medication use during pregnancy; (5) missing all lipid test data during pregnancy; and (6) loss to follow-up or unknown pregnancy outcomes. The final analysis included 25,081 participants (Supplemental Fig. 1). In accordance with the Declaration of Helsinki, studies involving humans were reviewed and approved by the Research Ethics Committee of Fujian Maternal and Child Health Hospital (approval number: 2017KR-030). The participants provided written informed consent to participate in this study.

Data collection

A questionnaire survey was used to collect the following data in the first trimester: maternal age, pre-pregnancy body mass index (BMI), height, abdominal circumference, education level, blood pressure, ethnicity, conception method, smoking status, number of pregnancies, alcohol consumption status, GDM status, and gestational hypertension (GH) status. Venous serum samples were taken after fasting for more than 8 h at 9–12 weeks of pregnancy, 22–26 weeks of pregnancy, and 30–34 weeks of pregnancy and during the delivery period (37–40 weeks).

Lipid measures

Maternal lipid profiles were measured in the laboratory of Fujian Provincial Maternity and Child Health Hospital. TC, TG, LDL-C, HDL-C, Apo-A1, and Apo-B were measured using a Siemens Advia 2400 fully automated biochemistry analyser from Munich, Germany. For blood lipids repeatedly measured within the same trimester, the measurements closest to 12, 25, and 32 weeks gestation in the first, second, and third trimesters, respectively, were selected. The measurement closest to 3 days prior to delivery was selected for the delivery period. The coefficients of variation for both interassay and intra-assay measurements across all lipid indicators were estimated to be less than 2.5%.

Definitions of adverse pregnancy outcomes

(1) GDM: In China, pregnant women are required to undergo a 75-g oral glucose tolerance test (OGTT) during mid-pregnancy. The patients had to fast for 10 h before their blood was drawn. Venous blood

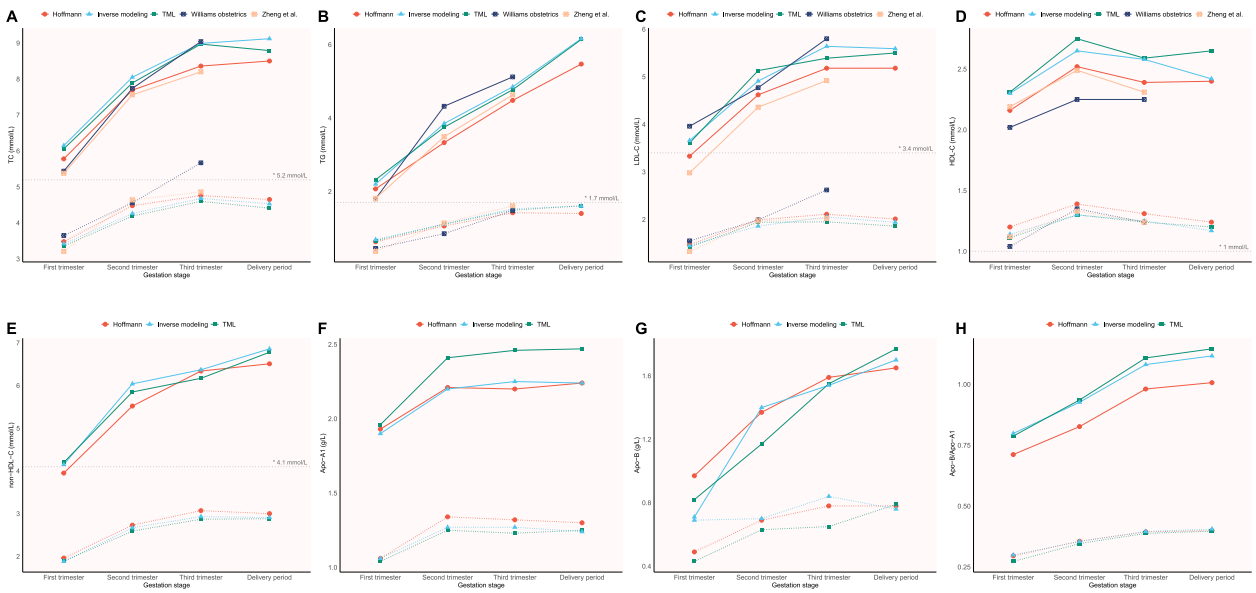

Fig. 1 Comparative analysis of TSRIs for maternal lipid profiles. The solid lines represent the upper limits of the TSRIs, and dashed lines represent the lower limits. The horizontal gray dashed line denotes the optimal lipid levels recommended by the "Chinese Guidelines for Lipid Management (2023)" [15]. Each figure tracks lipid and apolipoprotein markers from the first trimester to the delivery period, contrasting the approaches of the Hoffmann method, inverse modelling, and truncated maximum likelihood (TML) method, along with obstetrics references by Williams and findings from Zheng et al. [16]. (**A**) Total cholesterol (TC); (**B**) Triglyceride (TG); (**C**) Low-density lipoprotein cholesterol (LDL-C); (**D**) High-density lipoprotein cholesterol (HDL-C); (**E**) Non-high-density lipoprotein cholesterol (non-HDL-C); (**F**) Apolipoprotein A1 (Apo-A1); (**G**) Apolipoprotein B (Apo-B); (**H**) Apo-B/Apo-A1 ratio

samples were collected at 1 h, 2 h, and 3 h to determine blood glucose levels. The diagnostic criteria for GDM were as follows: fasting blood glucose levels > 5.1 mmol/L, > 10.0 mmol/L after 1 h, and > 8.5 mmol/L after 2 h [20].

(2) GH: A diastolic blood pressure (DBP) measured twice in the same arm ≥ 90 mmHg and/or a systolic blood pressure (SBP) ≥ 140 mmHg.
(3) PE: Hypertension after the 20th week of pregnancy, including symptoms such as headaches, dizziness, and vomiting.
(4) Preterm birth: Delivery at greater than 28 weeks but less than 37 weeks gestation.
(5) Low birth weight (LBW): A fetal birth weight < 2500 g.
(6) Macrosomia: A fetal birth weight ≥ 4000 g.
(7) SGA: A newborn birth weight less than 2 standard deviations below the average weight for the same gestational age.
(8) LGA: A newborn birth weight greater than the 90th percentile for the same gestational age.
(9) Birth defects: Embryos or fetuses may exhibit functional or structural abnormalities during pregnancy. The screening and identification of birth defects adhered to the Chinese National Criteria of Birth Defects and Tiny Deformities as delineated in the "Maternal and Child Health Monitoring Manual in China" and were coded according to the ICD-10 [21].

Statistical analysis

Frequencies and percentages are reported for categorical variables, and continuous variables regarding participant characteristics are presented as the means ± standard deviations. TSRIs were subsequently estimated via the TML, Hoffmann, and inverse modelling approaches (Supplemental Fig. 2). (1) TML method [22]: The German Society of Clinical Chemistry and Laboratory Medicine (DGKL) developed the 'Reference Limit Estimator' on the basis of the statistical program R. For simplicity of use, an Excel front end was designed, and the estimator is available online (https://www.dgkl.de). (2) Hoffmann method [23]: Outliers were deleted using the Chauvenet criterion. Next, a linear regression equation with the best fit was derived using the least squares method. Interpolation was then used to calculate the upper and lower limits of the reference interval: $RI_{min} = \alpha \times 2.5 + \beta$, $RI_{max} = \alpha \times 97.5 + \beta$. (3) Inverse modelling approach [24]: The latest algorithm was used to identify the model that best explained the original data to directly derive the reference interval. The package was an open-source R tool (https://cran.r-project.org/web/packages/refineR). On the basis of the comparison of the analysis results of this study and those of previous studies [16, 18], the TML method was selected as the primary method. Box plots and line graphs for eight lipid profiles were individually created for TSRIs, which were established by different methods.

Logistic regression was employed to examine how maternal lipid levels throughout pregnancy are related to APOs. In accordance with previous studies [16–18] and causal directed acyclic graphs (Supplementary Fig. 3), maternal age, alcohol consumption status, race, pre-pregnancy BMI, education level, smoking status, marital status, and thyroid hormone levels were adjusted for as potential clinical confounders during the first and second trimesters to assess the relationships between TSRIs and APOs. In addition, GDM was accounted for as a covariate during the third trimester and delivery period. R software 4.3.0 was used for the statistical analyses, with a two-sided significance criterion of $P \leq 0.05$. To address multiple comparisons, the Hochberg method was applied to the calibration P value.

Results

Baseline characteristics

Baseline data were collected from 25,081 pregnant women, and their clinical characteristics are presented in Table 1. The demographic composition was predominantly Han ethnicity (97.9%), with an average maternal age of 30.3 ± 4.0 years. Most pregnant women had a normal pre-pregnancy BMI (69.7%), while 12.1% were overweight before pregnancy, and 2.8% were obese. Furthermore, 78.0% of the subjects had a college degree or higher, 85.3% had never consumed alcohol, and 97.9% did not smoke. The proportions of women with GDM, GH, and PE were 23.0%, 3.1%, and 1.6%, respectively. Throughout pregnancy, all lipid parameters were significantly different ($P < 0.001$). LDL-C, non-HDL-C, Apo-B, TG, and TC levels gradually increased, whereas HDL-C and Apo-A1 levels exhibited minimal variation. The Apo-B/Apo-A1 ratio also tended to increase.

Establishing TSRIs using the TML, Hoffmann, and inverse modelling methods

The maternal levels of Apo-B, LDL-C, non-HDL-C, and TC increased approximately 1.5-fold, whereas TG levels increased 2.5-fold from the first trimester to the delivery period (Supplementary Fig. 4). The TSRIs for blood lipids established by the TML, Hoffmann, and reverse modelling methods are shown in Table 2. Overall, the upper reference values for Apo-A1, the Apo-B/Apo-A1 ratio, HDL-C, LDL-C, non-HDL-C, TC, and TG, which were calculated using the TML and reverse modelling methods, were higher than those determined by the Hoffmann method. Moreover, the distribution of pregnant women

Table 1 Baseline characteristics of participants by trimester group

Variables	Total (*n* = 25,081)	First trimester (*n* = 23,252)	Second trimester (*n* = 17,296)	Third trimester (*n* = 18,559)	Delivery period (*n* = 22,014)	*P* value
Age, years	30.3 ± 4.0	30.3 ± 4.0	30.3 ± 4.0	30.2 ± 4.0	30.3 ± 4.0	0.169
Abdominal circumference, cm	77.0 ± 12.0	77.0 ± 12.3	77.1 ± 12.1	77.0 ± 10.4	77.0 ± 12.5	0.87
SBP, mmHg	114.5 ± 11.2	114.6 ± 11.2	114.5 ± 11.3	114.6 ± 11.2	114.5 ± 11.1	0.75
DBP, mmHg	69.4 ± 9.8	69.4 ± 9.8	69.3 ± 10.1	69.4 ± 10.0	69.3 ± 9.8	0.853
Pre-pregnancy BMI, kg/m^2						0.984
Underweight	3707 (15.4)	3465 (15.4)	2557 (15.3)	2722 (15.2)	3269 (15.3)	
Normal weight	16,816 (69.7)	15,639 (69.6)	11,559 (69.3)	12,496 (69.8)	14,886 (69.8)	
Overweight	2922 (12.1)	2740 (12.2)	2087 (12.5)	2203 (12.3)	2582 (12.1)	
Obesity	678 (2.8)	632 (2.8)	468 (2.8)	491 (2.7)	588 (2.8)	
Married	23,722 (94.6)	22,008 (94.6)	16,358 (94.6)	17,598 (94.8)	20,934 (95.1)	0.083
Race-Han n (%)	24,517 (97.9)	22,734 (97.9)	16,909 (97.9)	18,154 (98.0)	21,538 (98.0)	0.961
Never smoke, n (%)	24,509 (97.9)	22,718 (97.8)	16,919 (98.0)	18,155 (98.0)	21,542 (98.0)	0.634
Never drink, n (%)	19,739 (85.3)	18,322 (85.3)	13,696 (85.5)	14,698 (85.5)	17,366 (85.5)	0.988
Education level, n(%)						0.087
Less than high school	2182 (8.7)	2024 (8.7)	1468 (8.5)	1494 (8.1)	1779 (8.1)	
Up to high school	3325 (13.3)	3079 (13.2)	2233 (12.9)	2412 (13.0)	2830 (12.9)	
College or higher	19,574 (78.0)	18,149 (78.1)	13,595 (78.6)	14,653 (79.0)	17,405 (79.1)	
Assisted reproduction, n (%)	1756 (7.1)	1611 (7.0)	1180 (6.9)	1307 (7.1)	1553 (7.1)	0.817
Pregnancy, n (%)						0.657
1	10,798 (43.5)	10,134 (43.8)	7520 (43.9)	8180 (44.4)	9529 (43.6)	
2	7472 (30.1)	6966 (30.1)	5186 (30.3)	5559 (30.2)	6631 (30.3)	
≥ 3	6579 (26.5)	6049 (26.1)	4427 (25.8)	4683 (25.4)	5692 (26.0)	
Parity, n (%)						0.423
0	14,954 (60.2)	13,932 (60.2)	10,373 (60.5)	11,243 (61.0)	13,098 (59.9)	
1	8830 (35.5)	8237 (35.6)	6057 (35.4)	6436 (34.9)	7835 (35.9)	
≥ 2	1065 (4.3)	980 (4.2)	703 (4.1)	743 (4.0)	919 (4.2)	
GDM, n (%)	5285 (23.0)	4889 (23.0)	3861 (23.8)	4358 (24.4)	5091 (23.3)	0.007
GH, n (%)	703 (3.1)	649 (3.1)	497 (3.1)	577 (3.2)	653 (3.0)	0.566
PE, n (%)	364 (1.6)	335 (1.6)	257 (1.6)	286 (1.6)	351 (1.6)	0.993
TC, mmol/L	5.8 ± 1.3	4.6 ± 0.7	6.1 ± 1.0	6.6 ± 1.1	6.6 ± 1.2	< 0.001
TG, mmol/L	2.2 (1.4, 3.1)	1.3 (1.0, 1.6)	2.1 (1.7, 2.6)	2.8 (2.3, 3.5)	3.2 (2.5, 4.1)	< 0.001
LDL-C, mmol/L	3.2 ± 1.0	2.4 ± 0.6	3.3 ± 0.8	3.7 ± 1.0	3.6 ± 1.0	< 0.001
HDL-C, mmol/L	1.8 ± 0.4	1.7 ± 0.3	2.0 ± 0.4	1.9 ± 0.3	1.8 ± 0.4	< 0.001
Non-HDL-C, mmol/L	4.0 ± 1.2	3.0 ± 0.6	4.1 ± 0.9	4.7 ± 1.0	4.8 ± 1.1	< 0.001
Apo-A1, g/L	1.7 ± 0.3	1.5 ± 0.3	1.8 ± 0.3	1.8 ± 0.3	1.8 ± 0.3	< 0.001
Apo-B, g/L	1.0 (0.8, 1.2)	0.7 (0.6, 0.8)	1.0 (0.9, 1.2)	1.2 (1.0, 1.3)	1.2 (1.0, 1.4)	< 0.001
Apo-B/Apo-A1	0.6 (0.5, 0.7)	0.5 (0.4, 0.6)	0.6 (0.5, 0.7)	0.7 (0.6, 0.8)	0.7 (0.6, 0.8)	< 0.001

Abbreviations: SBP systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *GDM* gestational diabetes mellitus, *GH* gestational hypertension, *PE* preeclampsia, *TC* total cholesterol, *TG* triglyceride, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Non-HDL-C* non-high-density lipoprotein cholesterol, *Apo-A1* apolipoprotein A1, *Apo-B* apolipoprotein B

Data are presented as mean ± standard deviation, median (interquartile range) or n (%). Due to the missing value, the sum of the numbers for categorical variables may be less than the total number of participants

considered to have levels out of the normal range of TSRIs was further analysed (Supplementary Table 1).

Comparative analysis of TSRIs for maternal lipid profiles

A comparative analysis focused on examining the trajectory of reference values for blood lipids throughout different trimesters (Fig. 1). The results revealed an overall increasing pattern in the concentrations of Apo-B, LDL-C, non-HDL-C, TC, and TG throughout pregnancy. Furthermore, an increasing trend across the entire pregnancy was observed for the Apo-B/Apo-A1 ratio. Conversely, the Apo-A1 level tended to be stable,

Table 2 Determine the reference range of blood lipids for each pregnancy using the truncated maximum likelihood method (TML), Hoffman method, and inverse modelling method

Methods	TC (mmol/L)	TG (mmol/L)	LDL-C (mmol/L)	HDL-C (mmol/L)	Non-HDL-C (mmol/L)	Apo-A1 (g/L)	Apo-B (g/L)	Apo-B/Apo-A1
TML								
First trimester	3.36—6.06	0.66—2.32	1.42—3.61	1.11—2.31	1.89—4.20	1.04—1.96	0.43—0.82	0.27—0.79
Second trimester	4.19—7.89	1.11—3.75	1.94—5.13	1.30—2.75	2.59—5.85	1.25—2.41	0.63—1.17	0.35—0.94
Third trimester	4.60—8.97	1.49—4.77	1.95—5.39	1.24—2.59	2.87—6.17	1.23—2.46	0.65—1.55	0.39—1.11
Delivery period	4.41—8.79	1.61—6.14	1.86—5.50	1.20—2.65	2.88—6.78	1.25—2.47	0.79—1.77	0.40—1.15
Hoffmann								
First trimester	3.48—5.78	0.63—2.07	1.47—3.33	1.20—2.16	1.96—3.95	1.06—1.93	0.49—0.97	0.30—0.71
Second trimester	4.48—7.69	1.06—3.33	1.99—4.62	1.39—2.52	2.73—5.52	1.34—2.21	0.69—1.37	0.36—0.83
Third trimester	4.76—8.36	1.42—4.48	2.11—5.18	1.31—2.39	3.07—6.34	1.32—2.20	0.78—1.59	0.39—0.98
Delivery period	4.65—8.50	1.40—5.47	2.01—5.18	1.24—2.40	3.00—6.51	1.30—2.24	0.78—1.65	0.40—1.01
Inverse modelling								
First trimester	3.42—6.15	0.69—2.20	1.45—3.66	1.14—2.30	1.88—4.15	1.06—1.90	0.69—0.71	0.30—0.80
Second trimester	4.26—8.05	1.11—3.85	1.86—4.91	1.30—2.65	2.67—6.04	1.27—2.20	0.70—1.40	0.35—0.93
Third trimester	4.68—8.99	1.53—4.85	2.05—5.64	1.25—2.58	2.93—6.37	1.27—2.25	0.84—1.54	0.40—1.08
Delivery period	4.53—9.12	1.60—6.16	1.94—5.59	1.17—2.42	2.91—6.86	1.24—2.24	0.76—1.70	0.41—1.12

Abbreviations: TG triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Non-HDL-C* non-high-density lipoprotein cholesterol, *Apo-A1* apolipoprotein A1, *Apo-B* apolipoprotein B, *TML* truncated maximum likelihood method

whereas the HDL-C level decreased during the second trimester.

Lipid levels beyond the TSRIs established by the TML method: Associations with APOs

The maternal lipid profiles outside of the TSRIs established by the TML method were associated with APOs (Tables 3, 4, 5 and 6). After adjustment for confounders, higher concentrations of Apo-A1, Apo-B, LDL-C, non-HDL-C, TC, and TG during the first trimester were found to increase the risk of GDM. Furthermore, elevated Apo-B and TG levels contributed to a greater risk of GH and PE. Pregnant women with lower TG levels during the second trimester were negatively associated with GDM and LGA, whereas those with elevated TG levels were at greater risk of GDM, GH, PE, LGA, and preterm birth. Moreover, decreased HDL-C and Apo-A1 levels significantly increased the risk of PE, LBW, and preterm birth. Reduced Apo-A1 and HDL-C levels during the third trimester increased the risk of PE, as did increased TG levels. Higher TG levels increased the risk of PE, LGA, and macrosomia, as did lower HDL-C levels. A strong positive correlation was identified between reduced Apo-A1, TC, and non-HDL-C levels during delivery and an elevated risk of APOs, such as LBW and preterm birth. Specifically, the odds ratio (OR) for lower TG levels was significantly greater at 2.83 (95% confidence interval [CI]: 2.20–3.64, $P_{adjust}=0.003$) for preterm birth and 3.33 (95% CI: 2.56–4.33, $P_{adjust}=0.003$) for LBW. Similar results were observed for the APOs associated with lipid levels outside the TSRIs established by the Hoffmann and reverse modelling methods (Supplementary Tables 2–9).

Discussion

This study established TSRIs for lipid profiles in singleton pregnant women in China utilizing the TML, Hoffmann, and reverse modelling methods. The TSRIs derived from the TML and reverse modelling methods closely match those of *Williams Obstetrics* but are higher than those of the Hoffmann method. Throughout pregnancy, the maternal lipid profiles of Apo-B, LDL-C, non-HDL-C, TC, and TG dramatically increase. Higher Apo-A1, Apo-B, LDL-C, non-HDL-C, TC, and TG levels during the first trimester are significantly associated with the occurrence of GDM. These observations collectively underscore the significant correlation between substantial variations in

Table 3 Comparing the association between the first trimester lipid levels and pregnancy outcomes based on truncated maximum likelihood (TML) estimation

Lipid profiles	Level	No. of cases	Model	GDM	GH	PE	LBW	Macrosomia	LGA	SGA	Preterm birth	Birth defects
TC	Higher	821	OR	**1.27 (1.08–1.49)**	1.39 (0.97–2.00)	1.38 (0.84–2.27)	1.17 (0.86–1.60)	0.83 (0.54–1.27)	0.98 (0.73–1.33)	0.83 (0.60–1.14)	**1.59 (1.24–2.04)**	1.09 (0.84–1.42)
			P Value	0.04	0.518	0.905	0.905	0.905	0.905	0.905	0.009	0.905
	Lower	571	OR	0.92 (0.74–1.15)	0.76 (0.43–1.35)	1.85 (1.06–3.23)	1.03 (0.69–1.54)	0.90 (0.54–1.50)	0.81 (0.53–1.24)	1.01 (0.72–1.43)	1.11 (0.78–1.58)	0.86 (0.61–1.23)
			P Value	0.934	0.934	0.27	0.934	0.934	0.934	0.934	0.934	0.934
TG	Higher	1091	OR	**2.03 (1.77–2.31)**	**1.53 (1.13–2.07)**	**2.62 (1.88–3.64)**	**1.44 (1.12–1.85)**	1.32 (0.99–1.78)	**1.45 (1.16–1.80)**	1.07 (0.82–1.41)	**1.71 (1.38–2.11)**	**1.39 (1.13–1.71)**
			P Value	0.006	0.018	0.006	0.016	0.124	0.006	0.62	0.006	0.01
	Lower	361	OR	**0.51 (0.36–0.72)**	0.37 (0.13–1.03)	1.72 (0.83–3.56)	1.04 (0.63–1.73)	0.61 (0.28–1.34)	0.65 (0.35–1.19)	1.56 (1.09–2.23)	0.81 (0.48–1.37)	0.73 (0.44–1.19)
			P Value	0.009	0.392	0.654	0.881	0.654	0.654	0.128	0.872	0.654
LDL-C	Higher	739	OR	**1.38 (1.17–1.64)**	1.54 (1.07–2.22)	1.72 (1.08–2.74)	1.33 (0.97–1.81)	0.85 (0.55–1.31)	0.90 (0.65–1.24)	0.71 (0.49–1.03)	1.45 (1.10–1.90)	1.25 (0.96–1.62)
			P Value	0.009	0.126	0.126	0.292	0.515	0.515	0.292	0.064	0.303
	Lower	699	OR	0.95 (0.78–1.16)	0.68 (0.39–1.18)	1.14 (0.61–2.13)	1.19 (0.84–1.69)	1.23 (0.81–1.87)	1.13 (0.80–1.59)	1.03 (0.76–1.41)	1.08 (0.78–1.50)	0.88 (0.64–1.21)
			P Value	0.847	0.847	0.847	0.847	0.847	0.847	0.847	0.847	0.847
HDL-C	Higher	579	OR	1.13 (0.93–1.37)	0.82 (0.48–1.40)	0.56 (0.23–1.36)	1.16 (0.81–1.67)	0.65 (0.36–1.15)	0.97 (0.67–1.41)	1.13 (0.82–1.54)	1.31 (0.96–1.80)	0.81 (0.57–1.14)
			P Value	0.876	0.876	0.876	0.876	0.876	0.876	0.876	0.792	0.876
	Lower	436	OR	1.09 (0.87–1.37)	1.08 (0.63–1.87)	**2.60 (1.55–4.35)**	1.32 (0.87–2.00)	1.37 (0.85–2.19)	1.26 (0.87–1.84)	1.20 (0.80–1.80)	1.42 (0.99–2.04)	1.13 (0.79–1.62)
			P Value	0.774	0.774	0.009	0.774	0.774	0.774	0.774	0.48	0.774
Non-HDL-C	Higher	859	OR	**1.52 (1.30–1.77)**	1.44 (1.02–2.04)	**1.90 (1.25–2.89)**	1.33 (0.99–1.77)	0.83 (0.55–1.25)	1.08 (0.82–1.43)	0.74 (0.53–1.04)	**1.81 (1.43–2.29)**	1.14 (0.88–1.47)
			P Value	0.008	0.234	0.021	0.285	0.578	0.578	0.324	0.008	0.578
	Lower	622	OR	0.86 (0.69–1.07)	0.65 (0.36–1.18)	1.07 (0.54–2.12)	0.92 (0.61–1.39)	0.90 (0.55–1.49)	0.84 (0.56–1.26)	0.83 (0.58–1.17)	1.10 (0.78–1.56)	1.04 (0.76–1.43)
			P Value	0.854	0.854	0.854	0.854	0.854	0.854	0.854	0.854	0.854
Apo-A1	Higher	1674	OR	**1.25 (1.11–1.40)**	0.94 (0.70–1.27)	0.57 (0.34–0.94)	0.85 (0.65–1.11)	1.05 (0.78–1.41)	1.12 (0.90–1.40)	0.90 (0.71–1.14)	1.14 (0.93–1.40)	**0.73 (0.59–0.91)**
			P Value	0.009	0.747	0.196	0.747	0.747	0.747	0.747	0.747	0.04
	Lower	448	OR	0.78 (0.60–1.10)	0.85 (0.46–1.56)	1.77 (0.96–3.26)	1.52 (1.04–2.24)	1.05 (0.61–1.80)	1.07 (0.71–1.62)	1.10 (0.74–1.63)	1.50 (1.04–2.16)	1.04 (0.71–1.52)
			P Value	0.357	0.864	0.402	0.264	0.864	0.864	0.864	0.252	0.864

Table 3 (continued)

Lipid profiles	Level	No. of cases	Model	GDM	GH	PE	LBW	Macrosomia	LGA	SGA	Preterm birth	Birth defects
Apo-B	Higher	4787	OR	**1.46 (1.35–1.57)**	**1.48 (1.24–1.76)**	**1.69 (1.34–2.14)**	1.14 (0.98–1.33)	1.04 (0.87–1.24)	1.09 (0.95–1.25)	0.91 (0.79–1.05)	1.19 (1.04–1.36)	1.07 (0.95–1.22)
			P Value	0.007	0.007	0.007	0.4	0.679	0.522	0.522	0.072	0.522
	Lower	492	OR	0.86 (0.67–1.1)	0.65 (0.33–1.30)	1.11 (0.51–2.43)	1.30 (0.88–1.92)	1.02 (0.61–1.72)	1.04 (0.69–1.56)	1.01 (0.70–1.44)	0.92 (0.61–1.40)	1.24 (0.89–1.72)
			P Value	0.964	0.964	0.964	0.964	0.964	0.964	0.964	0.964	0.964
Apo-B/Apo-A1	Higher	678	OR	1.19 (0.99–1.42)	1.56 (1.07–2.29)	**2.51 (1.64–3.82)**	1.41 (1.02–1.96)	1.23 (0.83–1.82)	1.08 (0.79–1.49)	1.28 (0.93–1.77)	1.46 (1.09–1.95)	**1.60 (1.23–2.06)**
			P Value	0.268	0.132	0.008	0.19	0.61	0.62	0.39	0.07	0.008
	Lower	390	OR	0.90 (0.69–1.18)	0.96 (0.51–1.80)	0.96 (0.39–2.34)	1.39 (0.90–2.16)	0.64 (0.30–1.37)	0.77 (0.44–1.32)	1.27 (0.86–1.88)	1.05 (0.68–1.62)	0.85 (0.56–1.30)
			P Value	0.929	0.929	0.929	0.929	0.929	0.929	0.929	0.929	0.929

Abbreviations: TG triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Non-HDL-C* non-high-density lipoprotein cholesterol, *Apo-A1* apolipoprotein A1, *Apo-B* apolipoprotein B, *OR* odds ratio, *GDM* gestational diabetes mellitus, *GH* gestational hypertension, *PE* preeclampsia, *LBW* low birth weight, *LGA* large for gestational age, *SGA* small for gestational age

The model adjusts for maternal age, pre-pregnancy BMI, education, race, smoking, drinking, marital status, and thyroid hormone levels. *P*-values were adjusted using the Hochberg method for multiple comparisons

Table 4 Comparing the association between the second trimester lipid levels and pregnancy outcomes based on truncated maximum likelihood (TML) estimation

Lipid profiles	Level	No. of cases	Model	GDM	GH	PE	LBW	Macrosomia	LGA	SGA	Preterm birth	Birth defects
TC	Higher	786	OR	1.16 (0.98–1.38)	1.43 (0.98–2.08)	0.95 (0.52–1.73)	0.74 (0.51–1.07)	0.81 (0.52–1.27)	1.13 (0.84–1.52)	0.81 (0.59–1.10)	1.11 (0.82–1.49)	1.01 (0.77–1.33)
			P Value	0.696	0.549	0.926	0.742	0.926	0.926	0.926	0.926	0.926
	Lower	348	OR	1.05 (0.81–1.36)	**2.04 (1.28–3.27)**	1.32 (0.62–2.84)	1.17 (0.73–1.88)	0.81 (0.41–1.58)	1.02 (0.64–1.62)	0.94 (0.57–1.56)	1.30 (0.85–1.99)	1.17 (0.79–1.74)
			P Value	0.94	0.027	0.94	0.94	0.94	0.94	0.94	0.94	0.94
TG	Higher	701	OR	**1.71 (1.45–2.01)**	**2.03 (1.46–2.82)**	**2.92 (1.98–4.31)**	1.39 (1.03–1.88)	1.46 (1.02–2.07)	**1.65 (1.27–2.13)**	1.03 (0.74–1.44)	**1.50 (1.14–1.97)**	1.23 (0.94–1.61)
			P Value	0.006	0.006	0.006	0.108	0.108	0.006	0.849	0.02	0.254
	Lower	409	OR	**0.52 (0.37–0.71)**	0.80 (0.39–1.63)	1.02 (0.42–2.50)	1.37 (0.89–2.11)	0.10 (0.01–0.69)	**0.28 (0.11–0.68)**	1.17 (0.8–1.72)	1.11 (0.71–1.73)	1.09 (0.73–1.62)
			P Value	0.009	0.965	0.965	0.918	0.14	0.04	0.965	0.965	0.965
LDL-C	Higher	435	OR	1.04 (0.82–1.31)	1.42 (0.86–2.33)	0.95 (0.43–2.12)	0.72 (0.43–1.20)	0.94 (0.53–1.64)	1.35 (0.93–1.96)	0.94 (0.63–1.40)	0.96 (0.63–1.45)	1.08 (0.76–1.54)
			P Value	0.908	0.908	0.908	0.908	0.908	0.908	0.908	0.908	0.908
	Lower	602	OR	1.25 (1.04–1.52)	1.36 (0.89–2.08)	1.07 (0.56–2.03)	1.30 (0.92–1.83)	0.99 (0.62–1.58)	1.18 (0.84–1.65)	1.20 (0.85–1.69)	1.06 (0.75–1.49)	1.17 (0.87–1.58)
			P Value	0.171	0.964	0.964	0.964	0.964	0.964	0.964	0.964	0.964
HDL-C	Higher	334	OR	1.21 (0.93–1.56)	1.73 (1.02–2.94)	0.66 (0.21–2.07)	0.83 (0.48–1.43)	0.60 (0.27–1.36)	0.82 (0.48–1.41)	1.10 (0.73–1.64)	0.72 (0.42–1.24)	1.02 (0.68–1.54)
			P Value	0.921	0.378	0.921	0.921	0.921	0.921	0.921	0.921	0.921
	Lower	380	OR	1.15 (0.9–1.46)	1.39 (0.83–2.32)	**3.77 (2.37–6.00)**	**2.35 (1.65–3.34)**	**2.01 (1.29–3.12)**	**1.85 (1.31–2.61)**	1.15 (0.72–1.82)	**1.85 (1.30–2.62)**	1.40 (0.98–1.99)
			P Value	0.524	0.524	0.006	0.006	0.01	0.006	0.562	0.006	0.252
Non-HDL-C	Higher	659	OR	1.13 (0.94–1.35)	1.53 (1.03–2.26)	1.53 (0.90–2.58)	0.84 (0.57–1.23)	0.82 (0.51–1.32)	1.11 (0.80–1.54)	0.98 (0.71–1.35)	1.09 (0.79–1.51)	1.12 (0.85–1.50)
			P Value	0.879	0.315	0.879	0.879	0.879	0.879	0.879	0.879	0.879
	Lower	423	OR	0.98 (0.77–1.25)	1.62 (1.01–2.61)	0.97 (0.43–2.21)	1.28 (0.84–1.93)	0.62 (0.31–1.27)	0.67 (0.40–1.13)	1.38 (0.95–2.00)	1.21 (0.81–1.80)	1.4 (1.00–1.96)
			P Value	0.947	0.384	0.947	0.947	0.947	0.81	0.651	0.947	0.384
Apo-A1	Higher	86	OR	1.40 (0.87–2.25)	1.14 (0.36–3.64)	1.51 (0.37–6.20)	1.11 (0.45–2.76)	1.72 (0.69–4.28)	1.33 (0.61–2.91)	0.83 (0.33–2.06)	0.79 (0.29–2.16)	0.95 (0.41–2.18)
			P Value	0.904	0.904	0.904	0.904	0.904	0.904	0.904	0.904	0.904
	Lower	253	OR	0.75 (0.53–1.05)	0.53 (0.19–1.45)	**2.87 (1.50–5.51)**	**2.64 (1.72–4.07)**	0.87 (0.38–1.98)	0.98 (0.55–1.75)	1.08 (0.60–1.96)	**2.08 (1.34–3.23)**	**1.92 (1.28–2.88)**
			P Value	0.445	0.864	0.006	0.006	0.953	0.953	0.953	0.006	0.006

Table 4 (continued)

Lipid profiles	Level	No. of cases	Model	GDM	GH	PE	LBW	Macrosomia	LGA	SGA	Preterm birth	Birth defects
Apo-B	Higher	4490	OR	1.10 (1.01–1.19)	1.03 (0.84–1.27)	1.06 (0.80–1.39)	0.96 (0.82–1.13)	1.00 (0.82–1.21)	1.18 (1.02–1.36)	**0.80 (0.69–0.93)**	1.18 (1.02–1.36)	0.98 (0.86–1.12)
			P Value	0.174	0.977	0.977	0.977	0.977	0.174	0.036	0.174	0.977
	Lower	422	OR	1.04 (0.82–1.32)	1.27 (0.76–2.14)	0.97 (0.43–2.21)	1.17 (0.77–1.79)	0.89 (0.50–1.60)	1.14 (0.75–1.73)	1.14 (0.77–1.68)	1.23 (0.83–1.84)	1.13 (0.79–1.62)
			P Value	0.941	0.941	0.941	0.941	0.941	0.941	0.941	0.941	0.941
Apo-B/Apo-A1	Higher	426	OR	0.88 (0.68–1.12)	1.12 (0.64–1.96)	2.21 (1.26–3.89)	1.14 (0.74–1.75)	1.16 (0.69–1.97)	1.41 (0.97–2.05)	0.9 (0.58–1.38)	1.37 (0.94–2.00)	1.11 (0.78–1.60)
			P Value	0.701	0.701	0.054	0.701	0.701	0.544	0.701	0.679	0.701
	Lower	468	OR	1.17 (0.94–1.46)	0.99 (0.57–1.71)	0.73 (0.3–1.78)	1.06 (0.69–1.63)	1.29 (0.8–2.1)	1.12 (0.75–1.67)	1.44 (1.02–2.03)	1.2 (0.83–1.74)	0.85 (0.58–1.24)
			P Value	0.971	0.971	0.971	0.971	0.971	0.971	0.351	0.971	0.971

Abbreviations: TG triglyceride, *TC*, total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Non-HDL-C* non-high-density lipoprotein cholesterol, *Apo-A1* apolipoprotein A1, *Apo-B* apolipoprotein B, *OR* odds ratio, *GDM* gestational diabetes mellitus, *GH* gestational hypertension, *PE* preeclampsia, *LBW* low birth weight, *LGA* large for gestational age, *SGA* small for gestational age

The model adjusts for maternal age, pre-pregnancy BMI, education, race, smoking, drinking, marital status, and thyroid hormone levels. *P*-values were adjusted using the Hochberg method for multiple comparisons

Table 5 Comparing the association between the third trimester lipid levels and pregnancy outcomes based on truncated maximum likelihood (TML) estimation

Lipid profiles	Level	No. of cases	Model	GH	PE	LBW	Macrosomia	LGA	SGA	Preterm birth	Birth defects
TC	Higher	494	OR	1.07 (0.64–1.77)	1.70 (0.95–3.06)	0.94 (0.57–1.56)	0.77 (0.44–1.34)	0.88 (0.58–1.32)	0.88 (0.61–1.26)	1.07 (0.70–1.62)	1.35 (0.98–1.86)
			P Value	0.804	0.532	0.804	0.804	0.804	0.804	0.804	0.532
	Lower	520	OR	0.99 (0.61–1.63)	1.83 (1.07–3.11)	1.57 (1.04–2.35)	0.88 (0.54–1.45)	0.91 (0.62–1.31)	1.04 (0.72–1.50)	1.45 (1.02–2.07)	0.80 (0.54–1.18)
			P Value	0.982	0.208	0.217	0.982	0.982	0.982	0.222	0.982
TG	Higher	1074	OR	**1.65 (1.24–2.20)**	**3.30 (2.40–4.53)**	1.15 (0.83–1.59)	**1.65 (1.25–2.16)**	**1.73 (1.40–2.13)**	0.88 (0.67–1.16)	1.38 (1.07–1.79)	1.27 (1.01–1.60)
			P Value	0.005	0.005	0.416	0.005	0.005	0.416	0.052	0.129
	Lower	391	OR	0.54 (0.24–1.22)	1.24 (0.55–2.82)	1.62 (1.02–2.56)	0.6 (0.28–1.27)	0.62 (0.35–1.11)	**1.75 (1.26–2.41)**	1.03 (0.63–1.69)	0.58 (0.34–1.00)
			P Value	0.534	0.902	0.294	0.534	0.534	0.008	0.902	0.3
LDL-C	Higher	866	OR	0.96 (0.64–1.45)	1.18 (0.69–2.02)	0.70 (0.45–1.08)	0.81 (0.54–1.23)	0.90 (0.66–1.24)	0.94 (0.72–1.23)	0.74 (0.51–1.08)	1.24 (0.96–1.61)
			P Value	0.864	0.864	0.732	0.864	0.864	0.864	0.732	0.732
	Lower	457	OR	0.88 (0.51–1.51)	1.57 (0.87–2.84)	1.28 (0.80–2.05)	1.70 (1.15–2.53)	1.47 (1.06–2.04)	0.95 (0.63–1.43)	1.27 (0.86–1.88)	0.76 (0.50–1.16)
			P Value	0.797	0.797	0.797	0.072	0.14	0.797	0.797	0.797
HDL-C	Higher	407	OR	1.03 (0.59–1.81)	1.03 (0.45–2.33)	1.54 (0.98–2.41)	**0.15 (0.04–0.59)**	0.31 (0.15–0.66)	1.45 (1.05–2.00)	1.37 (0.90–2.08)	1.03 (0.70–1.53)
			P Value	0.944	0.944	0.305	0.049	0.016	0.138	0.584	0.944
	Lower	413	OR	1.27 (0.77–2.08)	**2.83 (1.73–4.64)**	1.72 (1.11–2.68)	**2.15 (1.48–3.14)**	**1.88 (1.38–2.56)**	1.01 (0.66–1.54)	**1.88 (1.32–2.69)**	1.03 (0.69–1.53)
			P Value	0.964	0.005	0.064	0.005	0.005	0.964	0.005	0.964
Non-HDL-C	Higher	1603	OR	1.00 (0.74–1.35)	1.32 (0.90–1.94)	0.94 (0.70–1.25)	0.86 (0.64–1.17)	1.02 (0.81–1.27)	0.84 (0.67–1.04)	0.93 (0.72–1.20)	1.09 (0.88–1.33)
			P Value	0.995	0.995	0.995	0.995	0.995	0.864	0.995	0.995
	Lower	362	OR	0.99 (0.55–1.78)	1.96 (1.06–3.64)	1.82 (1.16–2.86)	1.17 (0.69–1.98)	1.10 (0.72–1.67)	1.03 (0.67–1.59)	1.64 (1.10–2.45)	0.85 (0.54–1.35)
			P Value	0.981	0.192	0.08	0.981	0.981	0.981	0.112	0.981
Apo-A1	Higher	133	OR	1.10 (0.45–2.71)	1.44 (0.45–4.56)	1.69 (0.82–3.49)	1.42 (0.66–3.06)	1.17 (0.61–2.25)	1.02 (0.53–1.95)	1.12 (0.52–2.42)	0.10 (0.01–0.73)
			P Value	0.956	0.956	0.956	0.956	0.956	0.956	0.956	0.184
	Lower	262	OR	0.85 (0.4–1.81)	**3.17 (1.75–5.75)**	1.95 (1.16–3.27)	1.19 (0.64–2.20)	1.25 (0.79–2.00)	1.32 (0.84–2.08)	1.77 (1.11–2.81)	1.50 (0.98–2.29)
			P Value	0.668	0.008	0.077	0.668	0.668	0.668	0.096	0.315
Apo-B	Higher	1589	OR	1.10 (0.82–1.47)	0.96 (0.63–1.48)	0.70 (0.50–0.98)	1.04 (0.78–1.38)	0.99 (0.79–1.23)	0.81 (0.65–1.01)	0.83 (0.63–1.08)	0.94 (0.76–1.17)
			P Value	0.902	0.902	0.28	0.902	0.902	0.441	0.902	0.902
	Lower	158	OR	1.15 (0.50–2.63)	1.61 (0.59–4.40)	1.91 (0.90–3.65)	0.71 (0.26–1.92)	1.04 (0.54–1.99)	1.45 (0.83–2.54)	1.25 (0.63–2.46)	0.90 (0.46–1.77)
			P Value	0.905	0.905	0.408	0.905	0.905	0.905	0.905	0.905
Apo-B/Apo-A1	Higher	591	OR	1.22 (0.78–1.91)	1.34 (0.74–2.44)	0.77 (0.45–1.29)	1.34 (0.89–2.00)	1.25 (0.90–1.73)	0.60 (0.40–0.91)	0.89 (0.59–1.35)	1.22 (0.89–1.67)
			P Value	0.586	0.586	0.586	0.586	0.586	0.12	0.586	0.586
	Lower	451	OR	0.88 (0.50–1.54)	1.3 (0.66–2.56)	1.35 (0.85–2.17)	1.02 (0.61–1.70)	0.92 (0.61–1.40)	1.51 (1.08–2.11)	1.06 (0.69–1.64)	0.69 (0.44–1.09)
			P Value	0.94	0.94	0.94	0.94	0.94	0.128	0.94	0.763

Abbreviations: TG triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Non-HDL-C* non-high-density lipoprotein cholesterol, *Apo-A1* apolipoprotein A1, *Apo-B* apolipoprotein B, *OR* odds ratio, *GDM* gestational diabetes mellitus, *GH* gestational hypertension, *PE* preeclampsia, *LBW* low birth weight, *LGA* large for gestational age, *SGA* small for gestational age

The model adjusts for maternal age, pre-pregnancy BMI, education, race, smoking, drinking, marital status, thyroid hormone levels, and GDM. *P*-values were adjusted using the Hochberg method for multiple comparisons

Table 6 Comparing the association between the delivery period lipid levels and pregnancy outcomes based on truncated maximum likelihood (TML) estimation

Lipid profiles	Level	No. of cases	Model	LBW	Macrosomia	LGA	SGA	Preterm birth	Birth defects
TC	Higher	1062	OR	0.72 (0.50–1.06)	0.97 (0.68–1.39)	1.24 (0.96–1.60)	0.92 (0.71–1.19)	0.65 (0.46–0.92)	1.09 (0.85–1.40)
			P Value	0.428	0.865	0.428	0.865	0.084	0.865
	Lower	607	OR	**2.36 (1.72–3.25)**	1.20 (0.77–1.87)	1.08 (0.76–1.54)	1.15 (0.81–1.63)	**2.12 (1.59–2.83)**	0.97 (0.67–1.38)
			P Value	0.005	0.848	0.848	0.848	0.005	0.848
TG	Higher	972	OR	0.83 (0.58–1.18)	**2.11 (1.65–2.69)**	**2.12 (1.74–2.57)**	0.91 (0.69–1.19)	0.92 (0.70–1.23)	**1.36 (1.09–1.69)**
			P Value	0.586	0.005	0.005	0.586	0.586	0.024
	Lower	500	OR	**3.33 (2.56–4.33)**	**0.06 (0.01–0.39)**	**0.30 (0.15–0.58)**	**2.33 (1.84–2.94)**	**2.83 (2.20–3.64)**	1.17 (0.85–1.59)
			P Value	0.003	0.008	0.003	0.003	0.003	0.338
LDL-C	Higher	902	OR	**0.52 (0.33–0.82)**	0.93 (0.64–1.36)	1.15 (0.88–1.52)	0.85 (0.65–1.12)	0.73 (0.51–1.03)	1.05 (0.80–1.37)
			P Value	0.03	0.732	0.732	0.732	0.355	0.732
	Lower	548	OR	**1.68 (1.18–2.39)**	1.18 (0.76–1.82)	1.40 (1.03–1.91)	1.05 (0.74–1.50)	**1.81 (1.35–2.43)**	1.3 (0.96–1.76)
			P Value	0.02	0.786	0.136	0.786	0.006	0.264
HDL-C	Higher	141	OR	**2.26 (1.24–4.12)**	-	-	1.41 (0.82–2.43)	1.54 (0.83–2.87)	0.96 (0.49–1.89)
			P Value	0.048	-	-	0.864	0.86	0.951
	Lower	660	OR	**1.95 (1.44–2.65)**	**1.79 (1.28–2.49)**	**1.84 (1.43–2.37)**	0.77 (0.53–1.10)	**2.15 (1.66–2.77)**	1.25 (0.94–1.66)
			P Value	0.003	0.003	0.003	0.154	0.003	0.154
Non-HDL-C	Higher	1058	OR	0.70 (0.48–1.01)	1.08 (0.78–1.49)	1.29 (1.02–1.64)	0.77 (0.59–1.01)	0.79 (0.59–1.08)	1.11 (0.88–1.41)
			P Value	0.224	0.655	0.222	0.224	0.423	0.655
	Lower	562	OR	**2.22 (1.63–3.03)**	0.88 (0.54–1.44)	0.91 (0.63–1.32)	**1.48 (1.10–2.00)**	**1.76 (1.32–2.37)**	1.07 (0.77–1.49)
			P Value	0.005	0.669	0.669	0.036	0.005	0.669
Apo-A1	Higher	261	OR	1.02 (0.55–1.87)	0.84 (0.41–1.71)	0.89 (0.52–1.54)	1.26 (0.83–1.94)	0.94 (0.54–1.65)	0.11 (0.03–0.43)
			P Value	0.953	0.953	0.953	0.953	0.953	0.012
	Lower	604	OR	**2.73 (2.06–3.62)**	1.41 (0.95–2.09)	**1.47 (1.09–1.98)**	1.18 (0.86–1.61)	**2.25 (1.73–2.93)**	**1.60 (1.22–2.09)**
			P Value	0.004	0.18	0.036	0.299	0.004	0.004
Apo-B	Higher	813	OR	**0.51 (0.32–0.82)**	1.08 (0.75–1.56)	1.23 (0.94–1.62)	0.69 (0.50–0.94)	0.81 (0.58–1.14)	0.89 (0.67–1.19)
			P Value	0.036	0.674	0.516	0.1	0.674	0.674
	Lower	708	OR	**1.89 (1.41–2.54)**	0.82 (0.52–1.28)	0.92 (0.67–1.28)	1.36 (1.03–1.79)	1.64 (1.25–2.14)	1.04 (0.78–1.40)
			P Value	0.005	0.782	0.782	0.12	0.005	0.782
Apo-B/Apo-A1	Higher	672	OR	1.09 (0.74–1.60)	**1.68 (1.20–2.36)**	**1.66 (1.27–2.18)**	0.76 (0.54–1.07)	1.20 (0.87–1.66)	1.17 (0.87–1.56)
			P Value	0.673	0.015	0.006	0.472	0.6	0.6
	Lower	584	OR	**1.77 (1.27–2.46)**	0.48 (0.26–0.91)	0.68 (0.45–1.04)	**1.71 (1.31–2.24)**	1.44 (1.05–1.97)	0.75 (0.52–1.09)
			P Value	0.005	0.072	0.138	0.005	0.072	0.138

Abbreviations: TG triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Non-HDL-C* non-high-density lipoprotein cholesterol, *Apo-A1* apolipoprotein A1, *Apo-B* apolipoprotein B, *OR* odds ratio, *GDM* gestational diabetes mellitus, *GH* gestational hypertension, *PE* preeclampsia, *LBW* low birth weight, *LGA* large for gestational age, *SGA* small for gestational age

The model adjusts for maternal age, pre-pregnancy BMI, education, race, smoking, drinking, marital status, thyroid hormone levels, and GDM. *P*-values were adjusted using the Hochberg method for multiple comparisons

lipid levels (higher or lower) and the increased probability of APOs. These findings emphasize the importance of monitoring lipid concentrations as a strategy for the detection and intervention of potential pregnancy complications. Additionally, the establishment of TSRIs during the delivery period, along with the introduction of new markers for non-HDL-C levels and the Apo-B/Apo-A1 ratio, addresses a significant gap in the literature.

Numerous studies have established TSRIs specifically designed to improve lipid profile monitoring and evaluation during pregnancy. Research indicates that the upper limits of LDL-C, HDL-C, TC, and TG levels should remain below the 95th percentile, whereas a minimum threshold above the 5th percentile should be maintained for HDL-C levels [17, 25]. For example, Wang et al. [18] suggested that the reference ranges for TC, TG, LDL-C, and HDL-C in early and mid-pregnancy should be < 5.64 mmol/L and < 7.50 mmol/L, < 1.95 mmol/L and < 3.56 mmol/L, < 3.27 mmol/L and < 4.83 mmol/L, > 1.23 mmol/L and > 1.41 mmol/L, respectively, which are lower than the values reported in the present study. The reference intervals for LDL-C, HDL-C, TC, and TG levels established by Zheng et al. [16] using the Hoffmann method closely align with those identified in the present study, which employed the same method. The TML and inverse modelling methods were used to determine TSRIs for LDL-C, HDL-C, TC, and TG levels that closely align with the commonly used lipid reference intervals proposed by *Williams Obstetrics* [26]. In addition, the reference ranges for Apo-A1 and Apo-B levels calculated by the percentile method are higher than those established in the present study, which may be due to differences in genetics, diet, and sample size in a study from Germany [25]. At present, research specifically addressing the delivery period remains limited. The physiological and hormonal changes differ significantly between the third trimester and the delivery period, although both are considered final phases of pregnancy.

When dyslipidemia occurs, the risk of APOs increases significantly [27–29]. Hyperlipidemia, which is linked to insulin resistance and GDM, accelerates glucose conversion into lipids and fat growth, disrupting metabolic homeostasis and increasing lipid levels. Research indicates that women with dyslipidemia have an increased risk of preterm birth [30]. Placental esterase converts these lipids to fatty acids, increasing blood viscosity, causing placental fat and vascular damage, affecting placental and immune functions, and potentially leading to APOs [30–32]. Nonetheless, previous studies have inadequately evaluated critical gestational periods and lipid indicators [16–18]. The findings of this study further indicated that the first trimester and delivery period may be more crucial, with the TG level potentially serving as a key indicator. The effect of abnormal TSRIs on APOs primarily include GDM, abnormal fetal weight, and preterm birth, all of which have biologically explicable mechanisms. Moreover, GDM is a well-established risk factor for various APOs and is also associated with elevated TG levels [33]. The complex interactions between insulin resistance and lipid metabolism, in both GDM and type 2 diabetes, have been extensively studied in recent years [34–36]. Therefore, GDM may function not only as a confounding variable but also as a potential effect modifier in the relationship between elevated TG levels and other APOs.

A Gambian cohort study revealed that 2.7% and 1.3% reductions in LBW risk were associated with elevated HDL-C and TC levels, respectively [37]. Elevated levels of HDL-C, an important cardiovascular protective factor, also strongly correlate with a reduced risk of PE [38]. These results reinforce the association between lower maternal HDL-C levels during pregnancy and an increased risk of PE. Furthermore, higher Apo-B, LDL-C, non-HDL-C, TC, and TG levels during the first trimester were observed in participants who had a greater incidence of APOs. Decreased Apo-A1 and HDL-C levels in the second trimester were related to APOs, including PE, LBW, macrosomia, and preterm birth. Reduced HDL-C in the third trimester was correlated with the incidence of PE, LGA, and macrosomia, whereas elevated TG levels were associated with an increased probability of these adverse outcomes.

An unexpected finding observed in this study was that both elevated and reduced HDL-C levels during the delivery period increased the risk of LBW. Although studies on the relationship between TSRIs during the delivery period and APOs are lacking, existing research suggests that decreased HDL-C levels may lead to greater susceptibility to LBW [37, 39]. The literature attributes the connection between lower HDL-C levels and APOs primarily to metabolic syndrome, oxidative stress, and the immune response [40–43]. Conversely, research from China indicates that elevated HDL-C levels in mothers close to delivery are tied to an increased likelihood of delivering SGA neonates [44]. Notably, elevated HDL-C is not universally beneficial, as dysfunctional HDL-C can contribute to APOs development [45, 46]. Notably, since APOs and lipid profiles were assessed simultaneously during the delivery period, this approach naturally restricts the capacity to determine causal relationships in this aspect of the study.

Apo-A1 and Apo-B, which are integral to lipoprotein functionality, play crucial roles in metabolism and conveyance. Apo-A1, which is primarily found in HDL-C, facilitates cholesterol efflux from peripheral tissues to the liver, thus reducing atherosclerosis risk [47]. Conversely,

Apo-B, a principal constituent of LDL-C, promotes the accumulation of lipoprotein particles within the arterial wall, increasing atherosclerosis susceptibility [48]. Previous research revealed that elevated Apo-B concentrations during the second trimester were correlated with an increased risk of preterm birth, whereas Apo-A1 levels were not significantly associated with an increased risk [14]. Interestingly, the findings of the present study revealed that reduced Apo-B levels and the Apo-B/Apo-A1 ratio during the delivery period increase the risk of LBW. Additionally, decreased levels of Apo-A1 in the second trimester may serve as a significant indicator of an elevated risk of PE, LBW, preterm birth, and birth defects.

A notable strength of this study is its utilization of a large prospective birth cohort, incorporating multiple statistical modelling methods and establishing reference intervals for eight lipid indices throughout pregnancy, including the delivery period. This research addresses gaps in the literature and provides comprehensive insights for standardizing lipid reference values during pregnancy. Nonetheless, several limitations warrant consideration. First, the single-centre design and predominantly Han Chinese cohort may limit the generalizability of the results. Second, while the final sample size remained statistically adequate after data exclusion (see Methods), the uneven distribution of lipid measurements across trimesters, particularly reduced second-trimester data due to variations in prenatal care schedules, may affect the precision of reference interval estimation. In addition, the absence of granular data on maternal lifestyle factors (e.g., dietary patterns, nutritional supplements, environmental exposures, and physical activity) and genetic polymorphisms introduces the possibility of residual confounding. However, this study prioritized adjustment for clinically significant confounders identified through available evidence, thereby minimizing the impact of unmeasured variables on outcome interpretation.

Conclusions

In conclusion, the TSRIs for blood lipid profiles in coastal areas of Southeast China were constructed using the TML, Hoffmann, and reverse modelling methods. These intervals are crucial for developing standardized blood lipid reference values during pregnancy. A complex association was also identified between inappropriate maternal lipid levels and the risk of APOs. This study contributes substantially to the accurate evaluation of blood lipid levels across pregnancy trimesters, facilitates the prevention of pregnancy complications, promotes maternal and neonatal well-being, and provides a comprehensive scientific basis for improving maternal and child health.

Abbreviations

Apo-A1	Apolipoprotein A1
Apo-B	Apolipoprotein B
APOs	Adverse pregnancy outcomes
BMI	Body mass index
GDM	Gestational diabetes mellitus
GH	Gestational hypertension
HDL-C	High-Density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
LGA	Large for gestational age
LBW	Low birth weight
Non-HDL-C	Non-high-density lipoprotein cholesterol
PE	Preeclampsia
SGA	Small for gestational age
TSRIs	Trimester-specific reference intervals
TC	Total cholesterol
TG	Triglyceride
TML	Truncated maximum likelihood

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Lili Yang, Zhaozhen Liu: study concepts and design, manuscript editing and manuscript preparation; Jiayi Chen, Chong Miao, Qingxiu Li: statistical analysis and experimental studies/data analysis; Jinying Chen, Wenjuan Liu, Haiyan Gao, Wei Li: literature research and clinical studies; Zhengqin Wu, Bin Sun, acquisition of data; Yibing Zhu, Haibo Li: guarantor of integrity of the entire study.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate

According to the Declaration of Helsinki, studies involving humans were reviewed and approved by the Research Ethics Committee of Fujian Maternal and Child Health Hospital (approval number: 2017KR-030). Participants provided written informed consent to participate in this study.

Competing interests

The authors declare no competing interests.

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