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Gestational Lipid Trajectories and Week-Specific Reference Intervals: A Real-World Longitudinal Cohort Study of 25,968 Pregnancies

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Abstract

Background

Maternal lipid metabolism undergoes substantial physiological adaptations throughout pregnancy. However, currently available lipid reference intervals are largely derived from nonpregnant populations or trimester-based cross-sectional studies and may not adequately reflect dynamic gestational lipid changes. We aimed to establish gestational week–specific continuous reference intervals for maternal serum lipids using longitudinal real-world data from a large Chinese cohort.

Methods

This retrospective longitudinal cohort study included pregnant women receiving prenatal care and delivering at a large tertiary women's and children's hospital in Southwest China between January and December 2024. Women with major pregnancy complications or preexisting dyslipidemia were excluded. A total of 25,968 women contributing 56,782 lipid measurements were included. Gestational week–specific percentiles for total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were estimated using quantile mixed-effects models with flexible nonlinear functions of gestational age. Classification discordance between the derived week-specific reference intervals and conventional lipid reference standards was evaluated.

Results

All lipid parameters demonstrated distinct nonlinear trajectories across gestation. Triglycerides showed the greatest increase, with the estimated 95th percentile rising from 2.54 mmol/L at 12 weeks of gestation to 7.37 mmol/L at 36 weeks. Compared with conventional Williams Obstetrics reference intervals, trimester-based criteria showed substantial classification discordance with the derived week-specific reference intervals, with 70.46% of measurements classified differently according to the prespecified comparison. In contrast, application of Chinese adult lipid criteria classified a high proportion of pregnant women as abnormal, with abnormal rates of 78.6% for TG, 67.8% for TC, and 42.4% for LDL-C. These findings demonstrate substantial discordance between conventional lipid classification systems and the observed gestational lipid distributions.

Conclusions

Maternal lipid profiles follow dynamic and nonlinear gestational trajectories that not fully captured by static trimester-based or adult reference standards. The gestational week–specific reference intervals established in this study provide a gestational age–specific framework that better reflects the observed variation in maternal lipid levels across pregnancy. Further studies are needed to externally validate

these reference intervals and determine their clinical relevance for maternal metabolic assessment and pregnancy-related outcomes.

1 Introduction

Maternal lipid metabolism undergoes substantial physiologic remodeling during pregnancy to support placental function, fetal growth, and maternal energy adaptation[1]. Increasingly, pregnancy is recognized as a dynamic metabolic state with potential implications for maternal and offspring cardiometabolic health across the life course[2, 3]. Within the Developmental Origins of Health and Disease (DOHaD) framework, maternal metabolic conditions during pregnancy may influence fetal metabolic programming through altered placental nutrient transport and intrauterine environmental exposure[4].

Physiologic gestational lipid changes are dynamic and substantial. Total cholesterol, triglycerides, and low-density lipoprotein cholesterol progressively increase throughout pregnancy, whereas high-density lipoprotein cholesterol typically rises initially and declines later in gestation. These adaptations are biologically necessary to support fetal development and maternal metabolic demands[5, 6]. However, distinguishing physiologic adaptation from potentially abnormal lipid elevation remains challenging because no universally accepted gestational week–specific lipid reference system currently exists.

Current gestational lipid assessment is limited by several structural deficiencies. First, lipid thresholds used in routine clinical practice are largely extrapolated from nonpregnant adult populations, although pregnancy represents a distinct and highly dynamic metabolic state[7, 8]. Because conventional adult lipid standards were developed primarily for long-term atherosclerotic cardiovascular disease risk stratification, applying these thresholds during pregnancy may overclassify physiologic metabolic adaptation as abnormal[9]. Second, obstetric lipid assessment commonly relies on trimester-based categorization, which artificially discretizes a biologically continuous metabolic process and assumes relative metabolic stability within each trimester[10]. Such assumptions may fail to capture rapid gestational lipid fluctuations during critical developmental windows. Third, widely used obstetric reference standards, including those from Williams Obstetrics, were predominantly derived from Western populations and may not be transferable to Chinese women because of differences in ethnicity, dietary structure, insulin resistance patterns, and cardiometabolic background. Existing Chinese studies have reported substantial disagreement between conventional obstetric thresholds and observed gestational lipid distributions, particularly for triglycerides[11, 12, 13, 14].

Increasing evidence suggests that gestational physiology is better characterized by continuous longitudinal trajectories rather than static phase-based thresholds[15, 16, 17]. This conceptual shift parallels a broader transition in modern obstetric medicine from isolated biomarker interpretation toward dynamic phenotyping and time-varying physiologic assessment[17]. In this framework, maternal lipid profiles may be more appropriately interpreted relative to gestational age–specific physiologic distributions

rather than fixed trimester cutoffs.

Using a large real-world longitudinal cohort from Southwest China, we characterized longitudinal gestational trajectories of total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol and established gestational week–specific continuous reference intervals across pregnancy. We further assessed the concordance of these trajectories with existing Williams Obstetrics reference ranges and Chinese adult lipid standards. By providing pregnancy-specific longitudinal reference data, this study aims to improve the physiologic interpretation of maternal lipid profiles and support future research on maternal metabolic health during pregnancy.

2 Methods

2.1 Study Design and Data Source

This retrospective longitudinal cohort study used routinely collected longitudinal data extracted from a dedicated obstetric electronic health record system at West China Second University Hospital, Sichuan University, a large tertiary academic women's and children's hospital and regional referral center in Southwest China, between January 1 and December 31, 2024.

2.2 Study Population

Among 28,918 women who delivered during the study period, 25,968 women contributing 56,782 lipid measurements were included in the primary analysis. Gestational age was estimated from the first day of the last menstrual period and confirmed by first-trimester ultrasonography.

To characterize physiologic gestational lipid trajectories, women with conditions known to substantially affect maternal lipid metabolism were excluded, including multiple gestations, preexisting dyslipidemia, gestational diabetes mellitus, hypertensive disorders of pregnancy, intrahepatic cholestasis of pregnancy, and major

fetal congenital anomalies.

Sensitivity analyses were conducted using alternative statistical modeling approaches to evaluate the robustness of the estimated gestational lipid trajectories.

2.3 Lipid Measurements

Fasting venous blood samples were collected during routine prenatal visits throughout gestation. Serum concentrations of total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were measured using enzymatic assays on the Beckman Coulter AU5800 automated analyzer (Beckman Coulter Inc). All laboratory analyses were conducted in the hospital's central clinical laboratory under standardized operating procedures with routine internal and external quality control.

2.4 Statistical Analysis

Gestational week–specific percentiles (P2.5, P5, P10, P25, P50, P75, P90, P95, and P97.5) for total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were estimated using quantile mixed-effects models with random intercepts to account for within-participant correlation from repeated measurements. Gestational age was modeled as a continuous variable from 0 to 42 weeks using natural cubic splines with 3 degrees of freedom to characterize nonlinear lipid trajectories across gestation.

Because individual women contributed repeated lipid measurements (range, 1–5 measurements; median, 2 measurements), mixed-effects modeling was selected to preserve longitudinal structure and estimate gestational age–specific lipid distributions. Sensitivity analyses were performed using ordinary quantile regression models with identical spline specifications treating observations as independent. Concordance between approaches was evaluated using concordance correlation coefficients and Bland-Altman analyses.

To evaluate clinical concordance with existing lipid classification systems, estimated percentile curves at 12, 24, and 36 gestational weeks were compared with trimester-specific reference ranges from Williams Obstetrics (25th edition). Underrecognition was defined as the proportion of lipid values classified as normal according to Williams criteria but exceeding the corresponding gestational age–specific reference limits derived from the study cohort. In parallel, median gestational lipid trajectories were compared with Chinese adult dyslipidemia thresholds for total cholesterol (≥ 5.18 mmol/L), triglycerides (≥ 1.7 mmol/L), low-density lipoprotein cholesterol (≥ 3.3 mmol/L), and high-density lipoprotein cholesterol (< 1.0 mmol/L).

All analyses were conducted using R software, version 4.3.1, with the lqmm, quantreg, and rms packages. Two-sided *P* values less than 0.05 were considered statistically significant. Ninety-five percent confidence intervals were estimated for gestational age–specific percentile curves.

3 Results

3.1 Beseline Characteristics

A total of 25,968 pregnant women contributing 56,782 lipid measurements were included in the primary analysis. The mean (SD) maternal age was 31.3 (3.6) years, 14,106 women (54.3%) were nulliparous, and the median (IQR) prepregnancy body mass index was 20.7 (3.5) kg/m². Most pregnancies were conceived naturally (23,929 [92.2%]). Additional baseline characteristics are summarized in Table 1.

Table 1
Baseline Characteristics of the Study Cohort

Characteristic	Total (N = 25,968)
Maternal age at delivery, mean (SD), y	31.32(3.64)
Age group, No.(%)	
< 25y	349 (1.34)
25-29y	8328 (32.07)
30-34y	12327 (47.47)
≥ 35y	4964 (19.12)
Method of Conception, No.(%)	
Natural Conception	23929 (92.15)
Assisted Reproductive Technology (ART)	2039 (7.85)
Menarche, mean(SD), y	12.75(0.87)
Pregnancy History, No.(%)	
First Pregnancy	14106 (54.32)
Second Pregnancy	8310 (32.00)
Three or More Pregnancies	3552 (13.68)
Prepregnancy BMI, M(IQR), kg/m^2	20.70(3.45)
BMI at First Prenatal Visit, M(IQR), kg/m^2	21.23(3.75)
Prepregnancy BMI category (WHO), No.(%)	
18.5–24.9 kg/m^2	19,679 (76)
< 18.5 kg/m^2	4,066 (16)
25-29.9 kg/m^2	2,014 (7.8)
≥ 30 kg/m^2	209 (0.8)
BMI at First Prenatal Visit category (WHO), No.(%)	
18.5–24.9 kg/m^2	19,772 (76)

Footnote: Continuous variables are presented as mean (SD) or median (IQR); categorical variables as No. (%). Percentages may not sum to 100 due to rounding. IQR indicates interquartile range; SD, standard deviation; WHO, World Health Organization.

Characteristic	Total (N = 25,968)
< 18.5 kg/m^2	2,992 (12)
25-29.9 kg/m^2	2,886 (11)
≥ 30 kg/m^2	318 (1.2)
Mode of Delivery, No.(%)	
Vaginal Delivery	8,885 (34)
Cesarean Section	16,609 (64)
Assisted Vaginal Delivery	474 (1.8)
Family History of metabolic disease, No.(%)	
Yes	4462(17.18)
No	21507(82.82)
Educational level, No.(%)	
Primary	62 (0.2)
Junior secondary	542 (2)
Senior secondary/Vocational	1,083 (4.2)
College/Undergraduate	18,801 (72.4)
Graduate or above	5,480 (21.1)

Footnote: Continuous variables are presented as mean (SD) or median (IQR); categorical variables as No. (%). Percentages may not sum to 100 due to rounding. IQR indicates interquartile range; SD, standard deviation; WHO, World Health Organization.

3.2 Maternal Lipid Trajectories Across Gestation

All lipid parameters demonstrated distinct nonlinear gestational trajectories, with increasing divergence across percentile distributions as pregnancy progressed (Fig. 1). Triglycerides showed the most pronounced gestational increase, particularly in the upper percentiles, with the 95th percentile increasing from 2.54 mmol/L at 12 gestational weeks to 7.37 mmol/L at 36 weeks. Total cholesterol and low-density lipoprotein cholesterol increased progressively throughout gestation, whereas high-density lipoprotein cholesterol demonstrated a biphasic trajectory characterized by an initial rise followed by a modest decline in late gestation.

The separation between lower and upper percentile curves became increasingly pronounced across gestation, particularly for triglycerides. Gestational week–specific percentile estimates are provided in eTables 1–4 in the Supplement.

Footnote

Gestational week–specific percentile trajectories (P2.5-P97.5) for (A) total cholesterol, (B) triglycerides, (C) high-density lipoprotein cholesterol, and (D) low-density lipoprotein cholesterol.

3.3 Comparison Between Gestational Lipid Trajectories and Williams Obstetrics Criteria

Substantial discordance was observed between gestational week–specific lipid trajectories estimated by quantile mixed-effects models and conventional Williams Obstetrics trimester-based reference ranges (Table 2; Figs. 2 and 3). Discordance patterns differed across lipid parameters and gestational stages.

The greatest discrepancies were observed for triglycerides. Across all trimesters, Williams criteria yielded substantially lower triglyceride thresholds than the gestational week–specific percentile estimates derived from the study cohort, particularly in early pregnancy. At 12 gestational weeks, the lower reference limit for triglycerides was 0.96 mmol/L using the study-derived trajectories compared with 0.45 mmol/L using Williams criteria, whereas the upper reference limit was 4.08 mmol/L vs 1.80 mmol/L, respectively.

In contrast, total cholesterol and low-density lipoprotein cholesterol showed relatively similar distributions in early gestation but progressively diverged in late pregnancy, with Williams criteria yielding substantially higher upper reference limits. At 36 gestational weeks, the upper limit for total cholesterol was 9.04 mmol/L according to Williams criteria compared with 7.58 mmol/L from the gestational trajectory–based estimates. Similar patterns were observed for low-density lipoprotein cholesterol. The magnitude and direction of these differences varied across lipid parameters and gestational stages.

Table 2
Discordance Between Gestational Lipid Percentile Trajectories and Williams Obstetrics Reference Ranges

Lipid parameter	Percentile	LQMM estimate, mmol/L (gestational week)	Williams reference, mmol/L (gestational age range)	Difference (LQMM – Williams), mmol/L	Relative difference, %
TC					
First trimester	P2.5	3.65 (12w)	3.65 (6 ~ 13w^{+6})	0	0
	P97.5	5.60 (12w)	5.44 (6 ~ 13w^{+6})	0.16	2.94
Second trimester	P2.5	4.81 (24w)	4.56 (14 ~ 27w^{+6})	0.25	5.48
	P97.5	6.77 (24w)	7.74 (14 ~ 27w^{+6})	-0.97	-12.53
Third trimester	P2.5	5.36 (36w)	5.67 (28w~delivery)	-0.31	-5.47
	P97.5	7.58 (36w)	9.04 (28w~delivery)	-1.46	-16.15
TG					
First trimester	P2.5	0.96 (12w)	0.45 (6 ~ 13w^{+6})	0.51	113.33
	P97.5	4.08 (12w)	1.80 (6 ~ 13w^{+6})	2.28	126.67
Second trimester	P2.5	1.52 (24w)	0.85 (14 ~ 27w^{+6})	0.67	78.82

Footnote: LQMM indicates linear quantile mixed model (with natural cubic splines to allow nonlinear trajectories). Williams reference ranges are from the 25th edition of *Williams Obstetrics*. Relative difference was calculated as (LQMM – Williams) / Williams × 100%. Gestational weeks (wk) for LQMM estimates were chosen to match the midpoint or typical timing of each Williams trimester category.

Lipid parameter	Percentile	LQMM estimate, mmol/L (gestational week)	Williams reference, mmol/L (gestational age range)	Difference (LQMM – Williams), mmol/L	Relative difference, %
	P97.5	4.66 (24w)	4.32 (14 ~ 27w^{+6})	0.34	7.87
Third trimester	P2.5	2.50 (36w)	1.48 (28w~delivery)	1.02	68.92
	P97.5	6.30 (36w)	5.12 (28w~delivery)	1.18	23.05
HDL-C					
First trimester	P2.5	1.38 (12w)	1.04 (6 ~ 13w^{+6})	0.34	32.69
	P97.5	2.09 (12w)	2.02 (6 ~ 13w^{+6})	0.07	3.47
Second trimester	P2.5	1.62 (24w)	1.35 (14 ~ 27w^{+6})	0.27	20
	P97.5	2.31 (24w)	2.25 (14 ~ 27w^{+6})	0.06	2.67
Third trimester	P2.5	1.50 (36w)	1.24 (28w~delivery)	0.26	20.97
	P97.5	2.18 (36w)	2.25 (28w~delivery)	-0.07	-3.11
LDL-C					
First trimester	P2.5	1.65 (12w)	1.55 (6 ~ 13w^{+6})	0.1	6.45

Footnote: LQMM indicates linear quantile mixed model (with natural cubic splines to allow nonlinear trajectories). Williams reference ranges are from the 25th edition of *Williams Obstetrics*. Relative difference was calculated as (LQMM – Williams) / Williams × 100%. Gestational weeks (wk) for LQMM estimates were chosen to match the midpoint or typical timing of each Williams trimester category.

Lipid parameter	Percentile	LQMM estimate, mmol/L (gestational week)	Williams reference, mmol/L (gestational age range)	Difference (LQMM – Williams), mmol/L	Relative difference, %
	P97.5	3.46 (12w)	3.96 (6 ~ 13w^{+6})	-0.5	-12.63
Second trimester	P2.5	2.35 (24w)	1.99 (14 ~ 27w^{+6})	0.36	18.09
	P97.5	4.19 (24w)	4.77 (14 ~ 27w^{+6})	-0.58	-12.16
Third trimester	P2.5	2.60 (36w)	2.62 (28w~delivery)	-0.02	-0.76
	P97.5	4.50 (36w)	5.80 (28w~delivery)	-1.3	-22.41

Footnote: LQMM indicates linear quantile mixed model (with natural cubic splines to allow nonlinear trajectories). Williams reference ranges are from the 25th edition of *Williams Obstetrics*. Relative difference was calculated as (LQMM – Williams) / Williams × 100%. Gestational weeks (wk) for LQMM estimates were chosen to match the midpoint or typical timing of each Williams trimester category.

Figure 2 illustrates substantial discordance between gestational week–specific lipid percentile trajectories and conventional Williams Obstetrics trimester-based reference ranges. For triglycerides and high-density lipoprotein cholesterol, Williams criteria consistently yielded lower reference limits across gestation. In contrast, for total cholesterol and low-density lipoprotein cholesterol, Williams criteria showed substantially higher upper limits during late pregnancy.

Footnote

Solid lines indicate gestational week–specific percentile trajectories (P2.5, P50, and P97.5), and dashed lines indicate trimester-based reference ranges from the 25th edition of Williams Obstetrics. Panels A through D correspond to total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, respectively.

Figure 3 demonstrates marked discordance between gestational week–specific lipid percentile trajectories and Williams Obstetrics reference ranges across gestation. For triglycerides, gestational trajectory–based estimates remained consistently higher than Williams thresholds at both lower and upper percentile limits throughout pregnancy, with the greatest divergence observed in early gestation. In

contrast, for total cholesterol and low-density lipoprotein cholesterol, discordance patterns shifted across gestation, with Williams criteria yielding progressively higher upper reference limits in late pregnancy. High-density lipoprotein cholesterol showed relatively modest but persistent differences between the 2 approaches.

Footnote

Points represent differences between gestational week–specific percentile estimates and Williams Obstetrics reference ranges at 12, 24, and 36 gestational weeks. Positive values indicate higher gestational trajectory–based estimates relative to Williams criteria, whereas negative values indicate lower estimates. Panels A through D correspond to total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, respectively.

3.4 Classification Discordance Between Gestational Lipid Trajectories and Williams Obstetrics Criteria

Substantial underrecognition of gestational lipid abnormalities was observed when Williams Obstetrics reference ranges were applied relative to gestational trajectory–based percentile estimates (Tables 3 and 4). The greatest discordance was observed for triglycerides, for which 520 of 738 abnormalities identified by gestational trajectory–based estimates (70.46%) were classified as normal according to Williams criteria. Underrecognition was also common for low-density lipoprotein cholesterol (48.55%), high-density lipoprotein cholesterol (43.17%), and total cholesterol (32.05%).

Table 3
Underrecognition of Gestational Lipid Abnormalities by Williams Obstetrics Criteria

Lipid parameter	Total Observations	Abnormal According to Gestational Trajectory Estimates, No.	Classified as Normal by Williams Criteria, No. (%)
TC	51418	1429	458(32.05)
TG	51418	738	520(70.46)
HDL-C	51418	2219	958(43.17)
LDL-C	51418	1483	720(48.55)

Footnote: Williams criteria were based on trimester-specific reference ranges from the 25th edition of Williams Obstetrics.

In contrast, overclassification rates were substantially lower across all lipid parameters. The highest overclassification rate was observed for triglycerides (12.94%), whereas rates for total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol remained below 6%. Overall, discordance patterns were characterized predominantly by underrecognition rather than overclassification.

Table 4
Overclassification of Gestational Lipid Abnormalities by Williams Obstetrics Criteria

Lipid parameter	Total Observations	Normal According to Gestational Trajectory Estimates, No.	Classified as Abnormal by Williams Criteria, No. (%)
TC	51418	4525	190(4.2)
TG	51418	4921	637(12.94)
HDL-C	51418	4114	206(5.01)
LDL-C	51418	4972	44(0.88)

Footnote: Williams criteria were based on trimester-specific reference ranges from the 25th edition of Williams Obstetrics.

3.5 Comparison Between Gestational Lipid Trajectories and Chinese Adult Lipid Thresholds

(1) Gestational Lipid Trajectories Relative to Adult Thresholds

Figure 4 demonstrates substantial discordance between physiologic gestational lipid trajectories and conventional Chinese adult lipid thresholds. Median total cholesterol and triglyceride levels exceeded adult thresholds during mid-pregnancy and continued to increase throughout gestation. Median low-density lipoprotein cholesterol levels similarly crossed adult thresholds during late second trimester and remained elevated thereafter. In contrast, median high-density lipoprotein cholesterol levels remained consistently above the adult lower threshold throughout gestation.

Footnote: Solid lines represent median (P50) levels for (A) total cholesterol (TC), (B) triglycerides (TG), (C) high-density lipoprotein cholesterol (HDL-C), and (D) low-density lipoprotein cholesterol (LDL-C). Horizontal dashed lines indicate adult thresholds: TC ≥ 5.18 mmol/L, TG ≥ 1.7 mmol/L, HDL-C < 1.0 mmol/L, LDL-C ≥ 3.3 mmol/L.

(2) Abnormal Classification Using Chinese Adult Lipid Thresholds

Application of conventional Chinese adult lipid thresholds resulted in high rates of abnormal lipid classification across pregnancy (Table 5). Triglycerides showed the highest abnormal classification rate, with 40,409 of 51,418 measurements (78.6%) exceeding adult thresholds. Total cholesterol and low-density lipoprotein cholesterol were similarly classified as abnormal in 67.8% and 42.4% of measurements, respectively. No high-density lipoprotein cholesterol measurements fell below the adult lower threshold.

Table 5
Abnormal Classification Rates Using Chinese Adult Lipid Thresholds

Lipid parameter	Total tests, No.	Total abnormal, No. (%)	Borderline high, No.	High, No.	Very high, No.
HDL-C	51,418	0 (0)	0	0	0
LDL-C	51,418	21,823 (42.44)	11,352	7,328	3,143
TC	51,418	34,851 (67.78)	16,364	18,487	0
TG	51,418	40,409 (78.59)	8,956	28,617	2,836

Footnote: Abnormal definitions are from the Chinese Guidelines for the Prevention and Treatment of Dyslipidemia in Adults: TC ≥ 5.18 mmol/L (borderline high, 5.18–6.22 mmol/L; high, ≥ 6.22 mmol/L); TG ≥ 1.7 mmol/L (borderline high, 1.7–2.3 mmol/L; high, ≥ 2.3 mmol/L; very high, ≥ 5.6 mmol/L); LDL-C ≥ 3.3 mmol/L (borderline high, 3.3–4.1 mmol/L; high, ≥ 4.1 mmol/L); HDL-C < 1.0 mmol/L.

3.5 Sensitivity Analysis

Sensitivity analyses demonstrated high concordance between gestational lipid trajectories estimated using quantile mixed-effects models and alternative quantile regression approaches (Figs. 5 and 6 and eTables 2 and 3 in the Supplement). Median gestational trajectories showed near-complete agreement across modeling approaches for all lipid parameters, with concordance correlation coefficients exceeding 0.98.

Agreement remained high across central percentile ranges (P25-P75), whereas greater variability was observed at extreme percentiles, particularly for lower percentile estimates of low-density lipoprotein cholesterol. Detailed percentile-specific comparisons and supplementary trajectory plots are provided in eFigures 1–5 and eTables 2–3 in the Supplement.

Footnote

Solid lines represent LQMM estimates; dashed lines represent QR estimates. The two curves are nearly superimposable for all lipids.

Footnote

CCC values are shown for P2.5, P5, P10, P25, P50, P75, P90, P95, and P97.5. Dashed horizontal line at 0.90 indicates excellent agreement benchmark.

4 Discussion

In this large real-world longitudinal cohort of 25,968 pregnant women, we characterized gestational trajectories of total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol and established gestational week–specific continuous reference intervals across pregnancy. All lipid parameters demonstrated distinct nonlinear patterns, with triglycerides exhibiting the

greatest increase and the most pronounced widening of upper percentile distributions. Comparison with conventional Williams Obstetrics trimester-based reference ranges and Chinese adult lipid criteria revealed substantial discordance across gestation. Together, these findings suggest that static trimester-based and nonpregnant adult reference systems may not fully reflect the gestational age–dependent variation in maternal lipid distributions and support the value of characterizing lipid concentrations using pregnancy- and gestational age–specific reference distributions[17, 18].

The observed lipid trajectories are consistent with the well-described metabolic adaptations of pregnancy[19, 20]. Progressive increases in triglycerides, total cholesterol, and low-density lipoprotein cholesterol have been attributed to metabolic changes that support placental function and fetal growth[21, 22]. The biphasic pattern of high-density lipoprotein cholesterol, characterized by an early rise followed by late gestational decline, further underscores the time-varying nature of maternal lipid regulation[23, 24]. Our findings extend these observations by demonstrating that not only central lipid levels but also the distributions of lipid concentrations vary continuously with gestational age. This gestational dependence should be considered when interpreting maternal lipid measurements during pregnancy[25, 26].

Comparison with Williams Obstetrics criteria further demonstrated differences between trimester-based reference ranges and the gestational week–specific distributions observed in our cohort[17]. The most pronounced discordance was observed for triglycerides, for which Williams criteria classified a substantial proportion of trajectory-defined abnormalities as normal. In contrast, for total cholesterol and low-density lipoprotein cholesterol, Williams criteria yielded higher upper limits in late pregnancy than the corresponding gestational trajectory–based estimates. These differences varied in both magnitude and direction according to lipid parameter and gestational age. Such discordance may partly reflect the categorization of gestation into discrete trimesters despite continuous biological changes across pregnancy, as well as differences between the populations from which reference ranges were derived [27, 28]. Such discordance likely reflects both the artificial discretization of a continuous biological process and the limited transferability of reference ranges derived from different populations[29].

The comparison with Chinese adult lipid thresholds revealed a different but equally important form of discordance. Adult lipid standards classified a large proportion of pregnancy lipid measurements as abnormal, particularly for triglycerides and total cholesterol. This finding should not be interpreted as evidence that these women necessarily had pathologic dyslipidemia. Rather, it illustrates the potential limitations of directly applying thresholds developed primarily for cardiovascular risk assessment in nonpregnant adults to lipid measurements obtained during pregnancy [30, 31]. The marked gestational changes observed in our cohort further support consideration of gestational age when interpreting maternal lipid concentrations[32].

More broadly, these findings align with an emerging shift toward trajectory-based interpretation of physiologic biomarkers across medicine[17, 33].Pregnancy is increasingly recognized as a dynamic cardiometabolic stress test rather than a static physiologic state, and gestational lipid remodeling may

reflect both short-term metabolic adaptation and longer-term maternal cardiometabolic vulnerability[34, 35]. Within this context, isolated measurements interpreted using fixed thresholds may not capture the continuous variation observed across pregnancy. Gestational week–specific reference intervals provide a framework for interpreting an individual measurement relative to the distribution observed at the corresponding gestational age[36, 37]. Whether this approach improves identification of clinically meaningful lipid abnormalities or prediction of pregnancy-related outcomes remains to be established.

The present findings therefore have potential implications for gestational lipid assessment, while their clinical application requires further evaluation. Gestational week–specific reference intervals may facilitate identification of lipid measurements that fall outside the expected distribution for a given gestational age. However, statistical reference limits should not be interpreted as diagnostic or treatment thresholds. Prospective studies incorporating maternal and neonatal outcomes are needed to determine whether deviations from these gestational distributions are associated with clinically meaningful risks and whether trajectory-based assessment provides additional predictive value beyond existing clinical indicators[38, 39]. If validated in independent populations and linked to clinically relevant outcomes, gestational age–specific reference systems could ultimately inform longitudinal metabolic monitoring during pregnancy.

Strengths and Limitations

This study has several important strengths. First, to our knowledge, it represents one of the largest longitudinal investigations of maternal lipid profiles during pregnancy, including 25,968 women and 56,782 lipid measurements. Second, the use of quantile mixed-effects models enabled the construction of gestational week–specific continuous reference intervals while accounting for repeated measurements and nonlinear gestational changes. Third, the real-world clinical data provided a comprehensive characterization of physiologic lipid trajectories across pregnancy and allowed direct comparison with commonly used obstetric and adult lipid reference standards.

Several limitations should also be acknowledged. First, this was a single-center retrospective cohort study conducted in Southwest China, and the derived reference intervals require external validation in geographically, ethnically, and clinically diverse populations before broader application. Second, pregnancies complicated by major metabolic or obstetric disorders and women with preexisting dyslipidemia were excluded to characterize lipid distributions in pregnancies without these conditions; therefore, the findings should not be generalized to higher-risk populations. Third, although gestational lipid distributions were comprehensively characterized, we did not evaluate associations between the derived reference intervals or trajectory deviations and maternal or neonatal outcomes. Consequently, the proposed reference intervals should be regarded as statistical reference distributions rather than clinical diagnostic or intervention thresholds. Fourth, the retrospective design limited the availability of potentially relevant behavioral, nutritional, genetic, and metabolic factors, and residual confounding or unexplained variation cannot be excluded. Finally, because the data were derived from routine clinical practice, the timing and frequency of lipid measurements were not standardized across participants,

although the longitudinal modelling approach accounted for repeated measurements obtained at different gestational ages.

Conclusions

In this large longitudinal cohort of pregnant women, maternal lipid profiles demonstrated marked and nonlinear changes across gestation, with substantial discordance observed between gestational lipid trajectories and commonly used trimester-based obstetric reference ranges as well as adult lipid thresholds. The gestational week–specific reference intervals established in this study provide a more detailed characterization of gestational age–dependent lipid variation and a framework for interpreting maternal lipid measurements according to gestational age. These findings provide a foundation for future studies to externally validate the derived reference intervals and evaluate the clinical relevance of gestational lipid trajectories in relation to maternal and offspring health outcomes.

Declarations

Acknowledgment

During the preparation of this manuscript, we used ChatGPT (OpenAI, GPT-4o, version 2024-05) to assist with language polishing and grammar checking. We take full responsibility for the integrity and accuracy of the final content.

Author Contributions

JP and HQ conceived the study, and JP, QL, HQ, and QW participated in the study design. QL and JP drafted the manuscript; YN, MQ, LS, and YH collected the samples and clinical data; and QL and QW performed the statistical analysis. HQ and QW supervised the study, and JP and HQ provided administrative and material support. HQ obtained the funding. JP and QL contributed equally to this work. All authors have read and approved the final manuscript.

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Declarations

Competing interests

The authors report no conflicts of interest.

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. This retrospective cohort study used exclusively pre-existing, anonymized clinical data extracted from electronic medical records. The research team had no access to directly identifiable patient information, and no additional patient contact or clinical intervention was involved. Under Article 32(2) of the *Measures for the Ethical Review of Life Sciences and Medical Research Involving Humans* (2023), issued by the National Health Commission of the People's Republic of China and other authorities, research using anonymized information data may be exempt from ethical review provided that it causes no harm to participants and does not involve sensitive personal information or commercial interests. Accordingly, this study was exempt from ethical review and therefore had no ethics approval reference number. Individual informed consent was not obtained because the study involved only secondary analysis of pre-existing anonymized data. All data were anonymized prior to analysis to protect participant privacy and data security.

Consent for publication

All authors have reviewed and approved the final manuscript for submission to this journal

Abbreviations

CCC	Concordance correlation coefficients
DOHaD	Developmental Origins of Health and Disease
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
LQMM	Linear quantile mixed model
QR	Quantile Regression
TC	Total cholesterol
TG	Triglycerides

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Figures

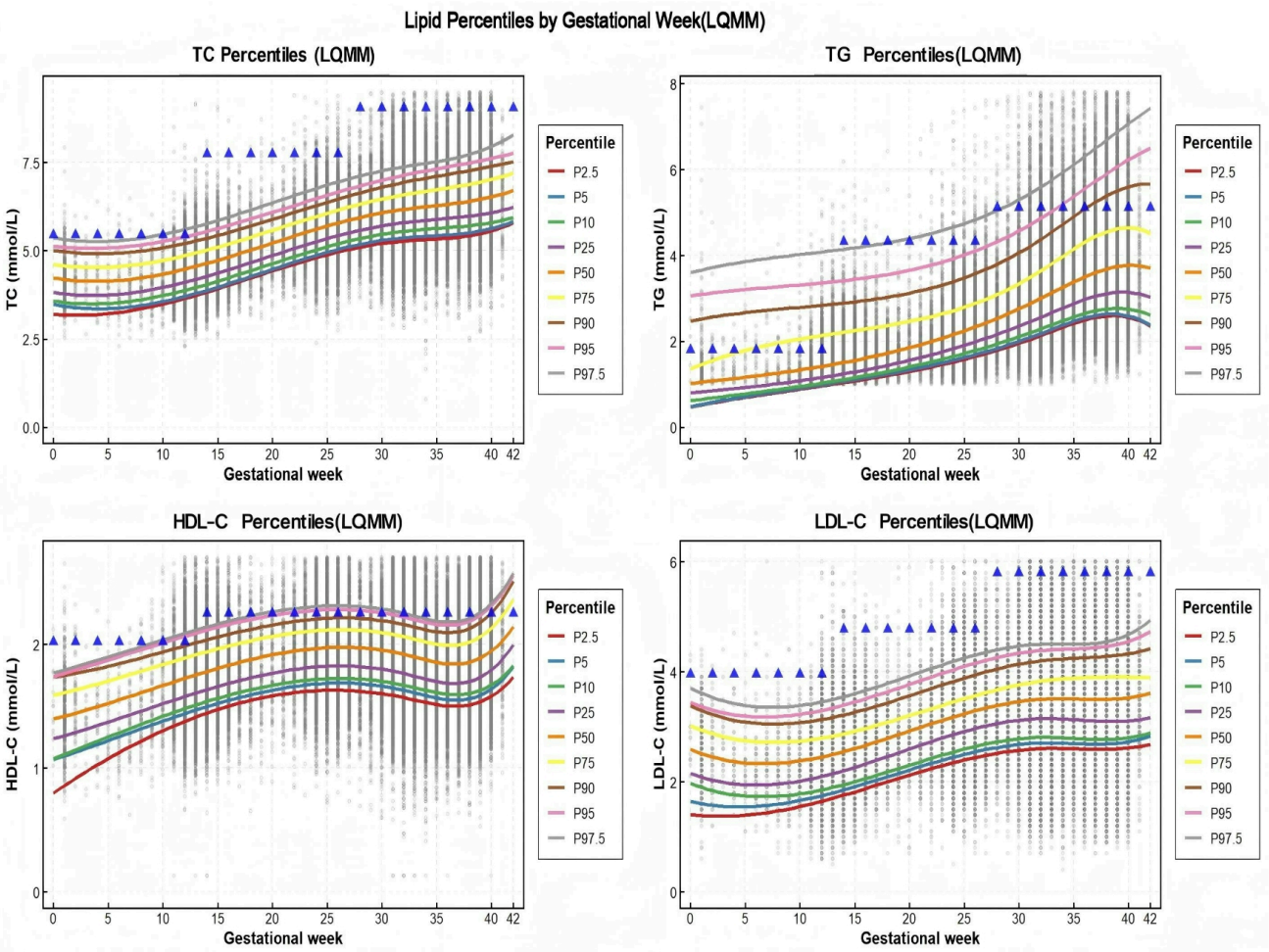

Figure 1

Gestational Week–Specific Percentile Trajectories of Maternal Lipids

Footnote: Gestational week–specific percentile trajectories (P2.5-P97.5) for (A) total cholesterol, (B) triglycerides, (C) high-density lipoprotein cholesterol, and (D) low-density lipoprotein cholesterol.

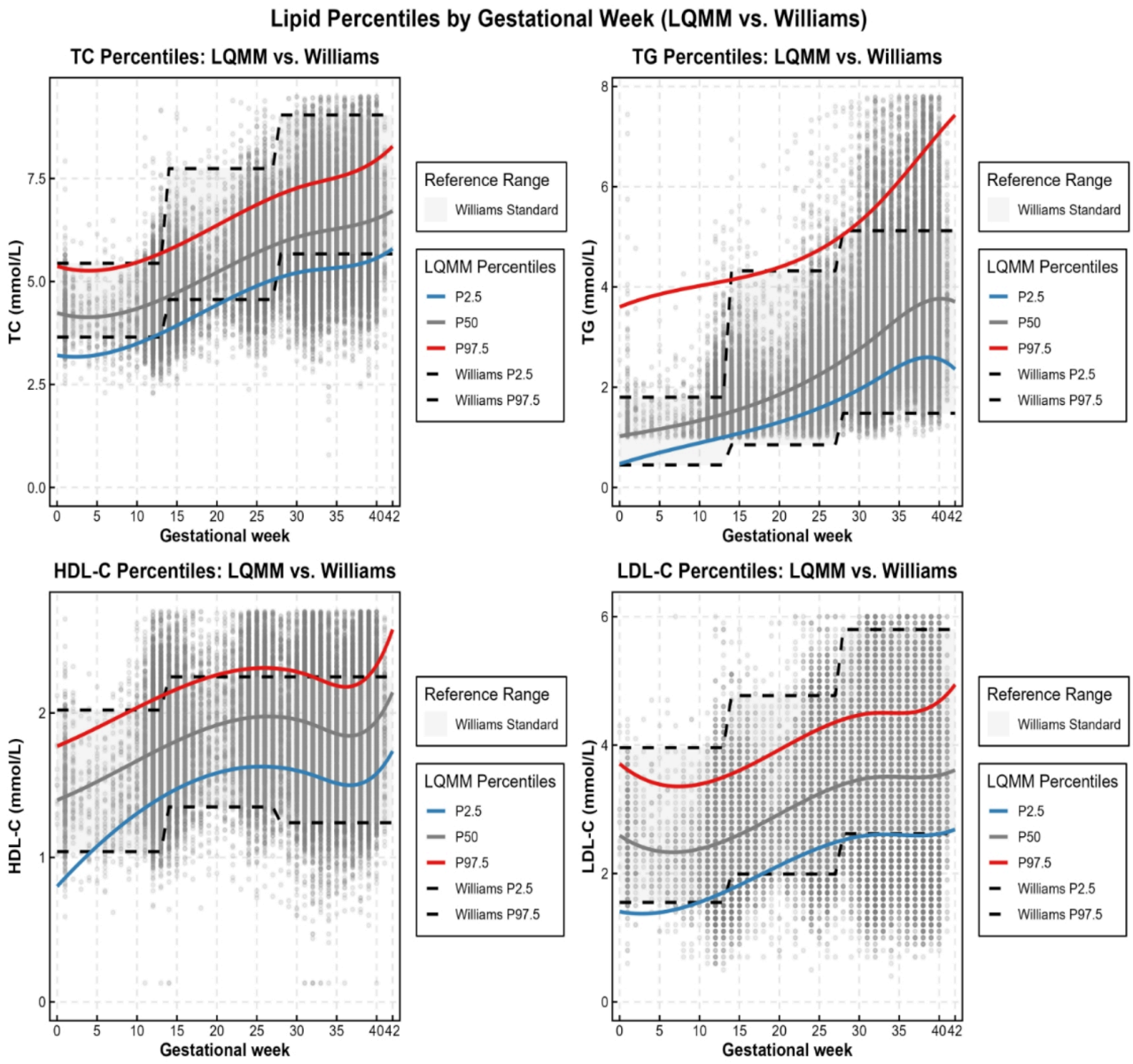

Figure 2

Discordance Between Gestational Lipid Percentile Trajectories and Williams Obstetrics Reference Ranges

Footnote: Solid lines indicate gestational week–specific percentile trajectories (P2.5, P50, and P97.5), and dashed lines indicate trimester-based reference ranges from the 25th edition of Williams Obstetrics. Panels A through D correspond to total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, respectively.

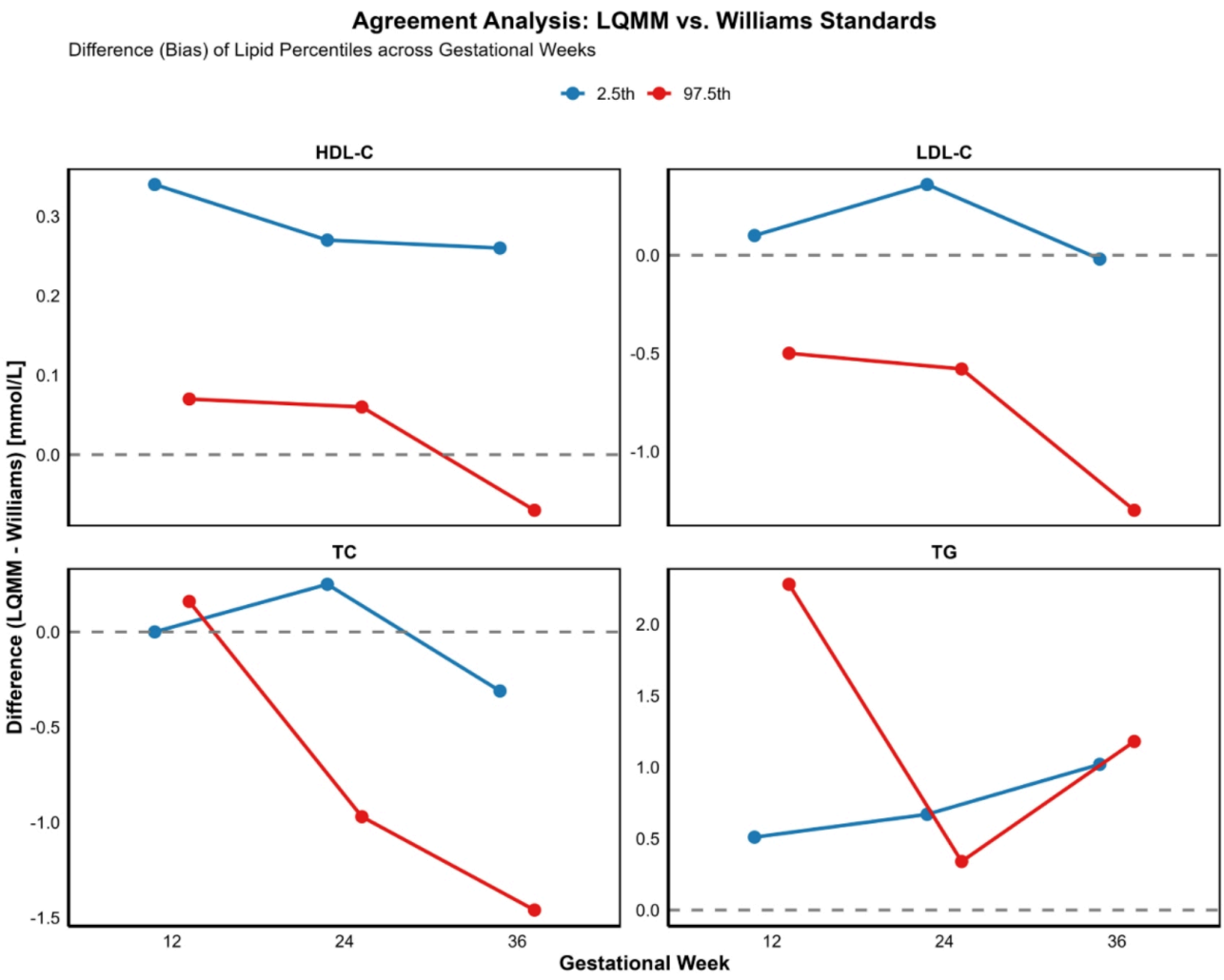

Figure 3

Discordance Between Gestational Lipid Percentile Estimates and Williams Obstetrics Reference Ranges

Footnote: Points represent differences between gestational week–specific percentile estimates and Williams Obstetrics reference ranges at 12, 24, and 36 gestational weeks. Positive values indicate higher gestational trajectory–based estimates relative to Williams criteria, whereas negative values indicate lower estimates. Panels A through D correspond to total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol, respectively.

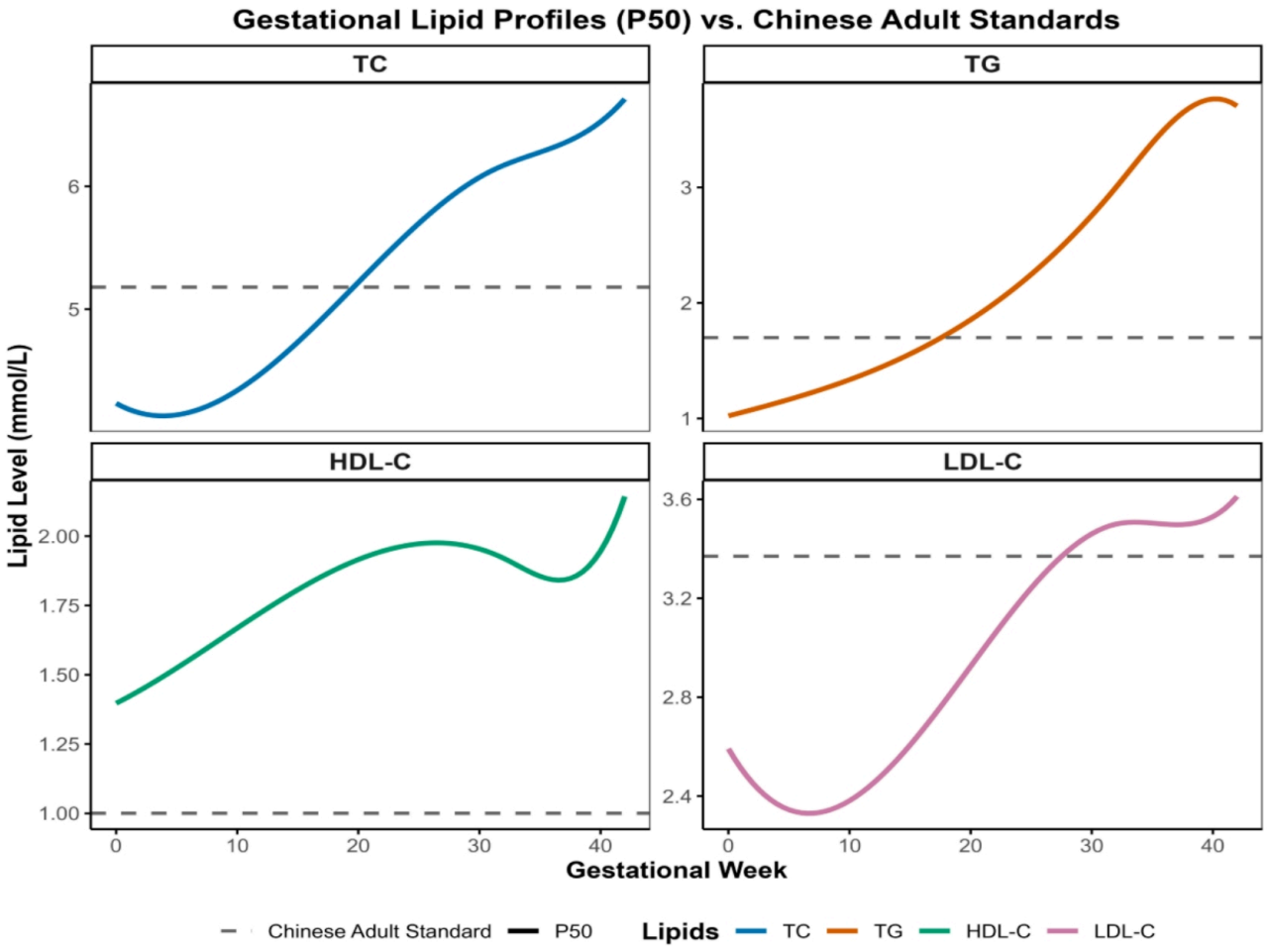

Figure 4

Discordance Between Gestational Median Lipid Trajectories and Chinese Adult Lipid Thresholds

Footnote: Solid lines represent median (P50) levels for (A) total cholesterol (TC), (B) triglycerides (TG), (C) high-density lipoprotein cholesterol (HDL-C), and (D) low-density lipoprotein cholesterol (LDL-C). Horizontal dashed lines indicate adult thresholds: TC ≥5.18 mmol/L, TG ≥1.7 mmol/L, HDL-C <1.0 mmol/L, LDL-C ≥3.3 mmol/L.

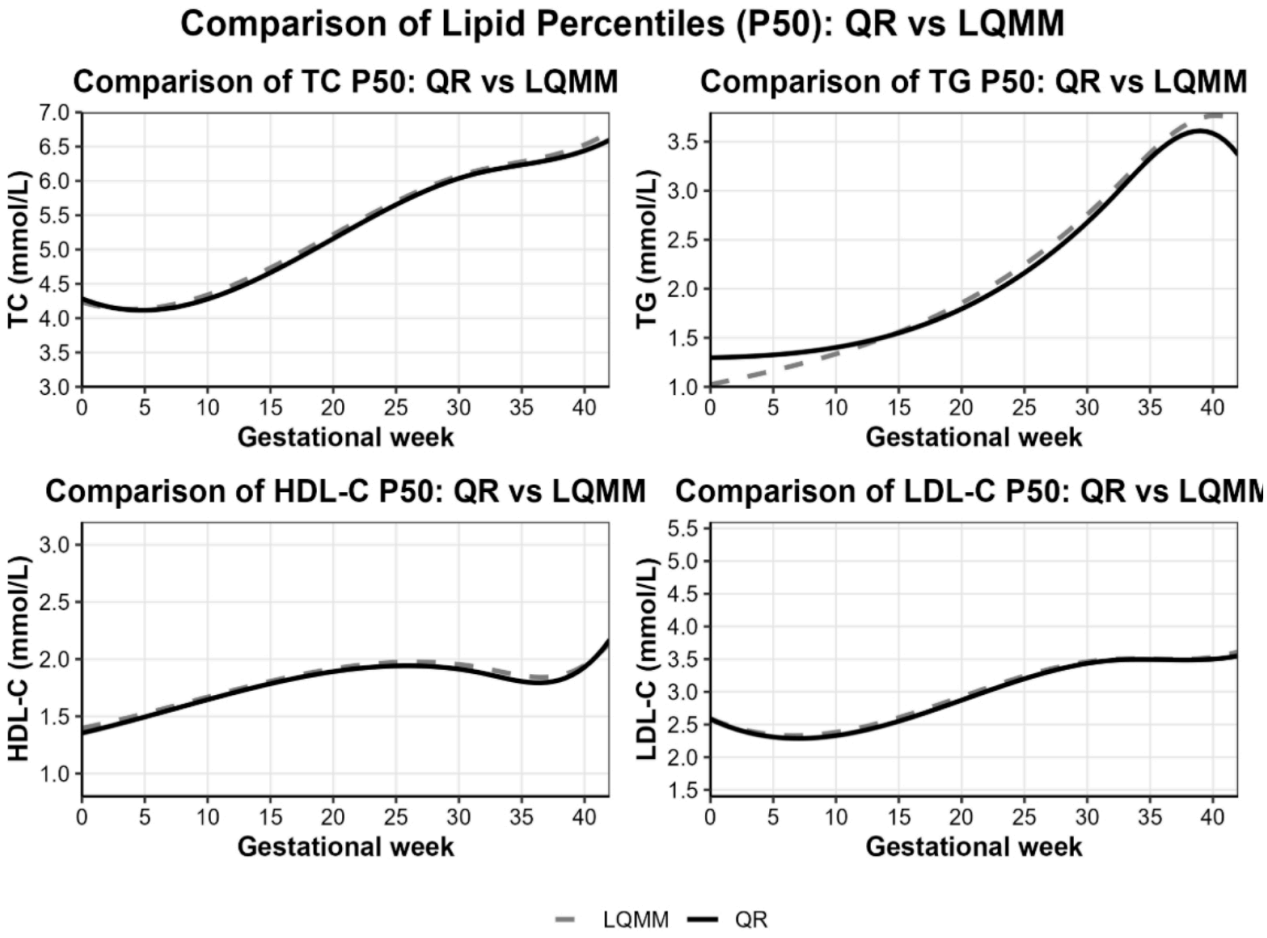

Figure 5

Comparison of LQMM and ordinary quantile regression (QR) estimates at the 50th percentile (P50) for (A) TC, (B) TG, (C) HDL-C, and (D) LDL-C

Footnote: Solid lines represent LQMM estimates; dashed lines represent QR estimates. The two curves are nearly superimposable for all lipids.

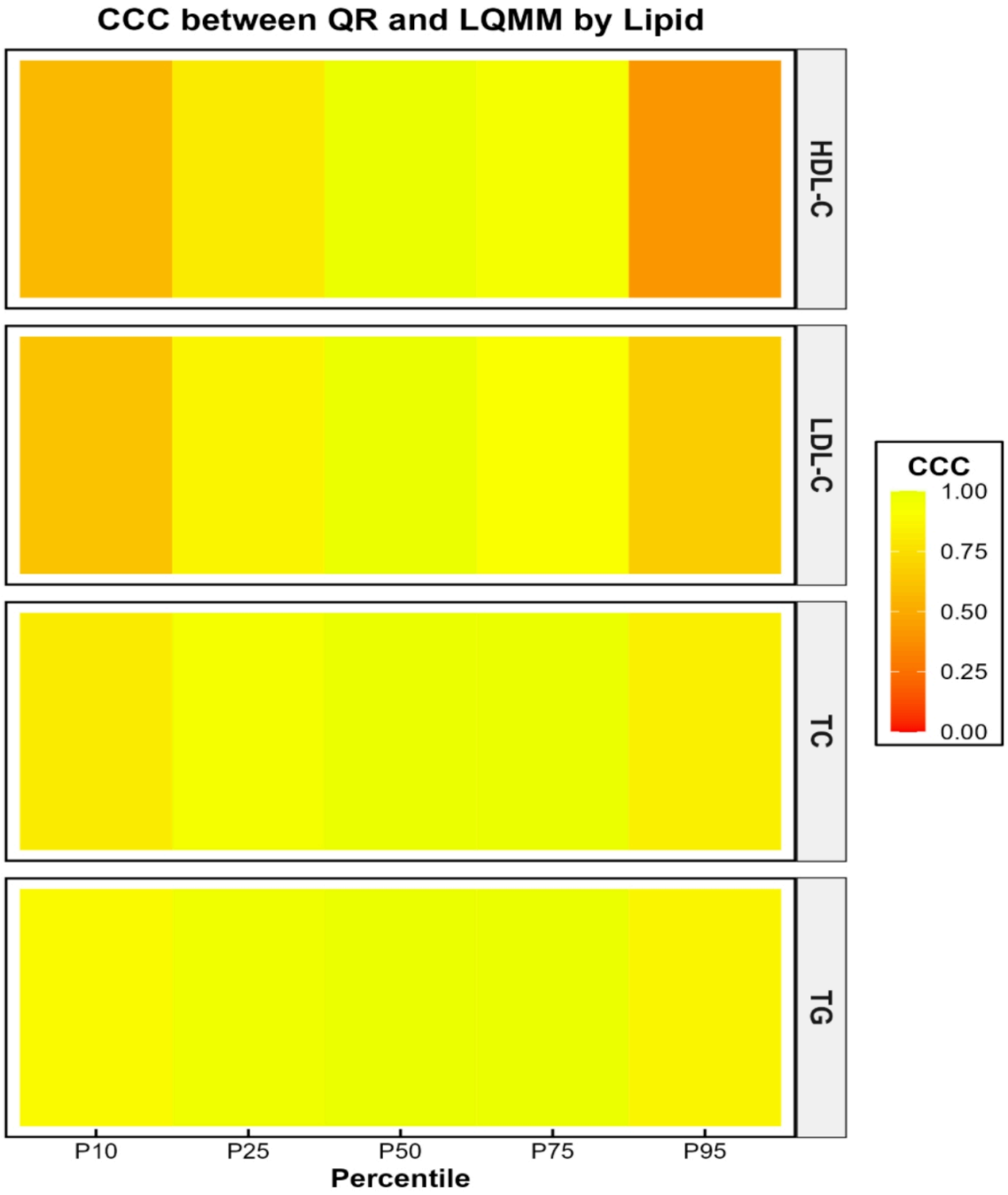

Figure 6

Concordance correlation coefficients (CCC) between LQMM and QR across percentiles for each lipid parameter

Footnote: CCC values are shown for P2.5, P5, P10, P25, P50, P75, P90, P95, and P97.5. Dashed horizontal line at 0.90 indicates excellent agreement benchmark.

Supplementary Files

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