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Lipoprotein particle concentration measured by nuclear magnetic resonance spectroscopy is associated with gestational age at delivery: a prospective cohort study

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Abstract

Objective—To estimate the association between lipoprotein particle concentrations in pregnancy and gestational age at delivery.

Design—Prospective cohort study

Setting—The study was conducted in the United States at the University of North Carolina.

Population—We assessed 715 women enrolled in the Pregnancy, Infection, and Nutrition study from 2001–2005.

Methods—Fasting blood was collected at two time points (<20 weeks and 24–29 weeks gestation). Nuclear magnetic resonance (NMR) quantified lipoprotein particle concentrations (low-density lipoprotein [LDL], high-density lipoprotein [HDL], very-low density lipoprotein [VLDL]) and 10 subclasses of lipoproteins. Concentrations were assessed as continuous measures,

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DETAILS OF ETHICS APPROVAL: The original PIN study was approved by the Institutional Review Board at the University of North Carolina at the time the study was performed. The present study utilized a de-identified dataset and was determined to be exempt by the UNC IRB.

with the exception of medium HDL which was classified as any or no detectable level, given its distribution. Cox proportional hazards models estimated hazard ratios (HR) for gestational age at delivery adjusting for covariates.

Main Outcomes Measures—Gestational age at delivery, preterm birth (<37 weeks gestation), and spontaneous preterm birth.

Results—At <20 weeks, three lipoproteins were associated with later gestational ages at delivery, (large LDL_{NMR} (HR 0.78, 95% CI 0.64, 0.96) total VLDL_{NMR} (HR 0.77, 95% CI 0.61, 0.98), and small VLDL_{NMR} (HR 0.78, 95% CI 0.62, 0.98), while large VLDL_{NMR} (HR 1.19, 95% CI 1.01, 1.41) was associated with a greater hazard of earlier delivery. At 24–28 weeks, average VLDL_{NMR} (HR 1.25, 95% CI 1.03, 1.51) and a detectable level of medium HDL_{NMR} (HR 1.90, 95% CI 1.19, 3.02) were associated with earlier gestational ages at delivery.

Conclusions—In this sample of pregnant women, particle concentrations of VLDL_{NMR}, LDL_{NMR}, IDL_{NMR}, and HDL_{NMR} were each independently associated with gestational age at delivery for all deliveries or spontaneous deliveries <37 weeks. These findings may help formulate hypotheses for future studies of the complex relationship between maternal lipoproteins and preterm birth.

Keywords

dyslipidemia; cholesterol; lipoproteins; gestational age at delivery; preterm birth; nuclear magnetic resonance spectroscopy

INTRODUCTION

Maternal metabolic changes in pregnancy increase fat storage and subsequent mobilization of these stores to support the growing fetus. In the second trimester, increasing estrogen, insulin, and insulin resistance increases maternal serum fatty acids and lipoproteins. The relationship between aberrations in lipid metabolism and adverse cardiovascular and metabolic outcomes in adults is well-described. In pregnant women, exaggerations in lipoproteins are associated with adverse pregnancy outcomes such as preeclampsia and gestational diabetes.^{1, 2} These pregnancy complications are known risk factors for future metabolic diseases.^{3, 4} Maternal dysmetabolic conditions may also enhance cardiovascular disease susceptibility in offspring.^{5, 6}

Preterm birth is the leading cause of morbidity and mortality among neonates without congenital anomalies in the United States.^{7, 8} Epidemiologic studies have demonstrated complex associations between maternal metabolic disease, preterm birth, and maternal risk of cardiovascular complications later in life.^{9–16} However, the mechanism linking metabolic exposures, pregnancy complications, and subsequent cardiovascular outcomes is not well understood. Previous studies associating maternal dyslipidemia with preterm birth risk vary by timing of sample collection, whether or not the patient was fasting, lipids measured, and the technique used to measure lipid concentrations. They also rely on traditional chemical techniques for measuring lipid concentrations that measure the cholesterol content of a person's low-density (LDL-C) and high-density (HDL-C) lipoprotein particles, but not the

absolute number of lipoprotein particles. Previous studies, thus, associated *lipid concentrations* and not *lipoprotein particle concentrations* with pregnancy outcomes.

Nuclear magnetic resonance (NMR) spectroscopy is an alternative method of measuring lipoproteins that relies on characteristic NMR signals of lipoprotein particles to quantify particle size and concentration.¹⁷ This is clinically relevant because chemically-measured lipoprotein lipid levels and NMR-measured lipoprotein particle numbers are not comparable. Two patients with the same lipid concentration may have vastly different amounts of particles in their serum, and thus different risk profiles¹⁸. Studies in non-pregnant patients have demonstrated that lipid particle concentrations measured by NMR have significant and independent associations with cardiovascular disease events regardless of lipid concentrations.^{19–21} NMR has been used in hundreds of studies in non-pregnant populations and has yielded new insight into the roles of particle subtypes in health outcomes. To date, only one study has reported the use of NMR to associate maternal dyslipidemia with preterm birth.²² However, this study was limited by the fact that it was a case-control study of women with a history of preterm birth, used samples from non-fasting patients, and had a different primary outcome. In addition, the investigators only had one sample for each patient and were not able to assess changes in lipids at two time points in pregnancy. The objective of our study was to use NMR to determine if lipoprotein particle concentrations at two points in pregnancy were associated with gestational age at delivery, specifically preterm birth and spontaneous preterm birth, in a cohort of pregnant women.

METHODS

Study population

The Pregnancy, Infection, and Nutrition Study (PIN) was a large, multiphase, cohort study whose primary aim was to identify etiologic factors for preterm delivery. The third phase of the study (PIN3) recruited women from prenatal clinics at the University of North Carolina before 20 weeks gestation from 2001–2005 (n=2006). Women were asked to complete the following: 2 research clinic visits (<20 weeks and 24–29 weeks gestation) and provide a fasting blood sample at each visit; 2 telephone interviews (17–22 weeks and 27–30 weeks gestation); and self-administered questionnaires at each clinic visit. Medical charts were abstracted following delivery. Women were excluded from participating in PIN3 if they were non-English speaking, <16 years old, carrying multiple gestations, not planning to continue care or deliver at the study hospital, or did not have a telephone for completing the interviews. The study protocols were approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Of those eligible, 967 (63%) women agreed to participate in the two research clinic visits and provide fasting blood samples and 755 (78.1%) consented to and had at least one blood sample drawn. We further excluded women missing data on gestational age at delivery (n=3) and those with a history of diabetes (n=37). The final sample included 715 women who provided at least one blood sample for analysis; 662 (92.6%) had two blood samples and 53 (7.4%) had one blood sample drawn during pregnancy.

Age, race, Hispanic ethnicity, education, and income were reported during the first telephone interview; the average number of cigarettes smoked in the first six months of pregnancy was reported during the second phone interview. Pre-pregnancy body mass index (BMI) was calculated from self-reported weight and measured height and categorized according to the Institute of Medicine's (2009) recommendations.²³ Gestational age was determined using both early ultrasound and last menstrual period. In the PIN study, 96% of participants had an ultrasound performed <22 weeks that was used to confirm the gestational age. Spontaneous preterm birth was based on clinical determination.

Lipoprotein particle analysis

Lipoproteins were measured by NMR Lipoprofile®-II autoanalyzer (formerly of Liposcience, Inc, Raleigh, NC, now Laboratory Corporation of America, Burlington, NC). This technology allowed for the assessment of each participant's lipoprotein subclass particle size (in nanometers) and concentration (particle nanomoles/L or $\mu\text{mol/L}$) and included total LDL_{NMR}, HDL_{NMR}, and VLDL_{NMR} and subclasses by particle size. It also provided calculated values for mean VLDL_{NMR}, LDL_{NMR}, and HDL_{NMR} particle size as well as total triglyceride levels. The laboratory determined the thresholds for particle size that were used to categorize the lipoprotein particle size and concentration measurements from each plasma sample into 16 subclasses, yielding up to 32 total assessments per participant.

Lipoprotein particle concentrations and sizes were assessed as continuous variables. Most women (70%) had no detectable medium HDL_{NMR} concentration at either time point and, as such, medium HDL_{NMR} was categorized as any or no detectable concentration.

Statistical analysis

Descriptive analyses were conducted to compare maternal and infant characteristics by preterm birth status. The associations between gestational age at delivery and lipoprotein particle concentrations, scaled to one standard deviation, were assessed using adjusted and unadjusted Cox proportional hazard models with gestational age as the time scale. Time varying coefficients were employed to estimate separate hazard ratios (HR) and 95% confidence intervals (CI) during the time period before and after 37 weeks of completed gestation, with HRs of delivery before 37 weeks of completed gestation being the target of inference. Adjustments were made for covariates identified a priori from the literature as being associated with either preterm birth or dyslipidemia, including age, race, education, income, pre-pregnancy BMI, and smoking. Each lipoprotein subclass was examined separately adjusting for other lipoprotein subclasses and triglycerides to estimate the direct effect of lipoproteins on preterm birth independent of other lipids. For example, LDL and VLDL models adjusted for total HDL and triglyceride concentrations while HDL models adjusted for total LDL and triglyceride concentrations. We considered lipoprotein particle concentrations measured at <20 weeks and those measured at 24–29 weeks separately. We also assessed the absolute change in lipoprotein particle concentrations between the two time points for all lipoproteins controlling for baseline concentrations, with the exception of medium HDL_{NMR}. We performed each of these analyses including all preterm births (defined as live births <37 weeks of gestation) and for spontaneous preterm births only.

We multiply imputed missing lipid data for those with only one blood sample (n=53 women) or missing covariate data (n=122) using Markov chain Monte Carlo methods (n=50 imputations). Analyses were performed using SAS 9.3 software (SAS Institute, Cary, North Carolina).

RESULTS

Women in our analytic sample were predominantly white, married, and had greater than a high school education. In addition, 32.2% had an income <185% of the poverty line, 21.0% were obese, and 10.3% smoked cigarettes <20 weeks. Birth outcomes included 100 (14.0%) preterm births and among those, 54 (7.6%) were spontaneous preterm births. Demographic information and characteristics of the sample, stratified by preterm birth outcomes, are presented in Table 1. Preterm deliveries were more common among black women, those with lower education and income, as well as a BMI indicative of underweight and overweight, compared with full term deliveries.

Mean particle concentrations and average particle sizes stratified by preterm birth status and timing of blood draw are listed in Table 2. Most lipids increase over the two time points regardless of preterm birth status, with the exception of medium HDL_{NMR}. In addition, particle size changes were much smaller in magnitude compared with particle concentration changes.

All Deliveries (Preterm and Term)

Adjusted hazard ratios for the association between lipoprotein particle concentrations and timing of delivery < 37 weeks are shown in Table 3 (unadjusted results are shown in Table S1). At <20 weeks, a one standard deviation change in large LDL_{NMR} particle concentrations (HR 0.78, 95% CI 0.64, 0.96) and total (HR=0.77, 95% CI 0.61, 0.98) and small (HR=0.78, 95% CI 0.62, 0.98) VLDL_{NMR} particle concentrations were associated with older gestational ages at delivery. At this same time point, a one standard deviation change in large VLDL_{NMR} particle concentrations was associated with an increased hazard of earlier delivery (HR=1.19, 95% CI 1.01, 1.41). At 24–28 weeks, these associations were not observed, however, the presence of a detectable level of medium HDL_{NMR} (HR=1.90, 95% CI 1.19, 3.02) and a one standard deviation change in average VLDL_{NMR} particle size (HR=1.25, 95% CI 1.03, 1.51) were associated with an increased hazard of earlier delivery at this time point. A one standard deviation change in total LDL_{NMR} from <20 to 24–28 weeks was associated with a hazard ratio of 0.76 (95% CI 0.60, 0.97), corresponding to older gestational ages at delivery.

The other time-varying coefficient in the Cox model described associations between lipoprotein particle concentrations and timing of term births. All 95% CIs for these variables included the null value of 1, indicating that lipid levels were unrelated to gestational age at delivery among term births (data not shown).

Spontaneous Deliveries (Preterm and Term)

Adjusted hazard ratios for the association between lipoprotein particle concentrations and timing of spontaneous preterm birth < 37 weeks are shown in Table 4 (unadjusted results are

shown in Table S2). At <20 weeks, a one standard deviation change in large LDL_{NMR} was associated with older gestational ages of spontaneous delivery (HR=0.73, 95% CI 0.55, 0.97). At 24–28 weeks, a one standard deviation change in total LDL_{NMR} (HR=0.67, 95% CI 0.48, 0.94) and IDL_{NMR} (HR=0.68, 95% CI 0.47, 0.98) particle concentrations were also associated with older gestational ages. The presence of a detectable level of medium HDL_{NMR} between 24–29 weeks was associated with an increased hazard of earlier spontaneous deliveries (HR=1.94, 95% CI 1.01, 3.75). A one standard deviation change in total LDL_{NMR} from <20 to 24–28 weeks was associated with a hazard ratio for spontaneous delivery of 0.59 (95% CI 0.41, 0.85) and thus older gestational ages.

All 95% CIs for associations between lipoprotein particle concentrations and timing of spontaneous delivery for term births included the null value of 1, indicating that lipid levels were unrelated to gestational age at delivery among term births (data not shown).

DISCUSSION

Main Findings

In this sample of pregnant women from the PIN cohort, we used NMR to perform advanced measurements of lipoprotein particle concentrations at two time points in pregnancy. NMR was further able to characterize subclasses of these particles that were associated with gestational age at delivery. We found that particle concentrations of VLDL_{NMR}, LDL_{NMR}, IDL_{NMR}, and HDL_{NMR} were each independently associated with gestational age at delivery for all deliveries or spontaneous deliveries <37 weeks. These associations were dynamic and dependent upon the time point in pregnancy at which they were assessed such that lipoprotein particle concentrations at <20 weeks had different associations with timing of delivery than those measured at 24–28 weeks. Higher particle concentrations of these lipoproteins at <20 weeks (small VLDL_{NMR}, total VLDL_{NMR}, large LDL_{NMR}) were associated with older gestational ages at delivery, but these associations were not observed between 24–28 weeks. Medium HDL_{NMR} was associated with earlier delivery at 24–28 weeks. Similar associations were observed with spontaneous delivery for large LDL_{NMR} (<20 weeks) and medium HDL_{NMR} (24–28 weeks) with additional associations observed with older gestational ages of spontaneous deliveries for total LDL and IDL. Medium HDL_{NMR} is a unique particle since most women did not have a detectable level. When treated as a dichotomous variable, we found that any detectable concentration of medium HDL_{NMR} was associated with earlier deliveries among all preterm and spontaneous preterm deliveries.

Strengths and Limitations

This study builds on prior studies by examining the association between lipoprotein particle concentrations and gestational age at delivery using an advanced method of lipoprotein measurement. The strengths of this study include the large prospective cohort design, medical records and birth outcomes readily available and abstracted by trained study personnel in a standardized manner, and the collection of fasting blood samples at two time points in pregnancy. The use of NMR to characterize lipoprotein particle concentrations has

only been reported once in a study of pregnant women and represents a novel way to investigate the association between dyslipidemia and adverse pregnancy outcomes.

There are limitations. Some measures (e.g. pre-pregnancy BMI, income, smoking) were self-reported and are subject to misclassification from recall. Confounding by unmeasured factors may have impacted the associations that were observed. The generalizability of this study may be limited because the women were recruited from one clinic in North Carolina and probably do not represent the general population. In addition, the women in our analytic sample were not necessarily representative of the original pregnancy cohort because of exclusion criteria, thus, selection bias may affect our results.

Interpretation

Previous studies have demonstrated associations between lipid concentrations and both spontaneous and indicated preterm birth. However, these studies did not assess lipid particle concentrations. In studies of non-pregnant populations, lipid concentration and particle concentration are not equivalent in their association with outcomes (i.e. cardiovascular disease risk).¹⁹ Thus, we sought to identify specific particles and particle concentrations that were associated with gestational age at delivery among women in our study.

In addition, previous studies varied in their methodology, such as the collection of non-fasting samples, assessment of different lipids, the technology used to measure concentrations, and outcome definitions. These differences make direct comparison to our results difficult. Prior studies have demonstrated conflicting results. For example, Catov et al. reported that mean concentrations of total cholesterol (from non-fasting samples) at <15 weeks were higher among women with preterm birth <34 weeks compared to those with term births.¹³ More recently, Mudd et al. reported increased odds of preterm birth among women with low total cholesterol, low HDL-C, and low LDL-C levels from non-fasting samples between 15–27 weeks gestation.²⁴

Similar to our observation that average VLDL_{NMR} (24–28 weeks) was associated with earlier gestational age at delivery, Thorp et al. observed an increased odds of recurrent PTB (<35 weeks) per nanometer increase in average VLDL_{NMR} particle size (OR 1.04, 95% CI 1.01, 1.08).²² Our finding that medium HDL_{NMR} was associated with an increased hazard of delivery before 37 weeks is also similar to the observation that medium HDL_{NMR} was associated with an increased odds of recurrent PTB in the Thorp et al. study. In contrast to the Thorp et al. study (in which statistically significant findings were only associated with an increased odds of recurrent preterm birth), we found several additional particles that were associated with a decreased hazard of delivery <37 weeks. Similar to our study, Thorp et al. reported a median medium HDL_{NMR} concentration of 0.1 among preterm birth cases and 0.0 among controls, suggesting that the majority of women in their study did not have a detectable medium HDL_{NMR} concentration as well. Direct comparison of results to the Thorp et al. study is limited by the fact that their study design (nested case-control), study population (patients with a history of a prior preterm birth), and primary outcome (delivery <35 weeks) were different than the present study. In addition, in the Thorp et al. study, all of the patients were exposed to 17-hydroxyprogesterone supplementation and a portion of the

patients were exposed to omega-3 fatty acid supplementation, which may explain some differences in results.

CONCLUSION

The association between maternal dyslipidemia and adverse pregnancy outcomes has been previously described in other studies, but there is great variability in the associations found and the manner in which the exposures and outcomes are defined. The mechanisms behind these associations have not been elucidated. Advanced measurements of lipid subclasses and lipoprotein particle concentrations using NMR represent an opportunity to investigate these associations more closely and may provide insight into the mechanism. Our study confirms the association between dyslipidemia and preterm delivery and expands the literature by identifying specific lipoprotein subclasses associated with gestational age at delivery in our sample. These findings may help formulate hypotheses for future studies of the complex relationship between maternal lipoproteins and preterm birth. Additional prospective studies using advanced measurements of lipoproteins are necessary to confirm these findings and may further elucidate underlying mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1
 Characteristics of pregnant women by preterm birth status (N=715), PIN Study, 2001–2005.

	Full Term Deliveries	All Preterm Deliveries	P-value	Spontaneous Preterm Deliveries Only			
Overall, n (%)	615	86.0	100	14.0	54	7.2	
Gestational age (mean, SD)	39.2	1.2	33.4	3.9	<0.0001	32.9	4.3
Maternal age (mean, SD)	28.8	5.5	28	6.5	0.28	26.8	6.4
Maternal age, n (%)					0.06		
24	144	23.4	28	28.0		19	35.2
25–29	172	28.0	32	32.0		14	25.9
30–34	213	34.6	21	21.0		14	25.9
35+	86	14.0	19	19.0		7	8.1
Maternal race & Hispanic ethnicity, n (%)					0.002		
Non-Hispanic white	461	75.0	62	62.0		35	64.8
Non-Hispanic black	103	16.8	32	32.0		16	29.6
Non-Hispanic other	50	8.1	6	6.0		3	5.6
Hispanic	0	0.0	0	0.0		0	0.0
Education, n (%)					0.0002		
Less than high school	42	6.8	10	10.0		5	9.3
High school graduate	77	12.5	26	26.0		18	33.3
Some college	122	19.8	24	24.0		11	20.4
College graduate	374	60.8	40	40.0		20	37.0
Income (% of poverty), n (%)					0.002		
<185%	113	18.4	32	32.0		21	38.9
185–350%	142	23.1	16	16.0		5	9.3
>350%	334	54.3	42	42.0		22	40.7
Pre-pregnancy body mass index, n (%)					0.02		
Underweight	26	4.2	8	8.0		6	11.1
Normal weight	342	55.6	41	41.0		23	42.6
Overweight	118	19.2	28	28.0		14	25.9
Obese	129	21.0	21	21.0		11	20.4

	Full Term Deliveries	All Preterm Deliveries	P-value	Spontaneous Preterm Deliveries Only
Prenatal cigarette smoking ^a , n (%)	61 9.9	13 13.0	0.15	8 14.8
Any MVPA ^b , n (%)	402 65.4	56 56.0	0.11	27 50.0
Nulliparous, n (%)	305 49.6	43 43.0	0.26	22 40.7
Delivered a low birth weight infant, n (%)	9 1.5	60 60.0	<0.0001	34 63.0
Delivered a SGA infant, n (%)	33 5.4	9 9.0	0.11	1 1.9

Abbreviations: SD, standard deviation; MVPA, moderate to vigorous physical activity; SGA, small-for-gestational age

NOTE: Data were missing for the following: race and Hispanic ethnicity (n=1), income (n=36), pre-pregnancy body mass index (n=2), prenatal cigarette smoking (n=51), MVPA (n=3), delivered a low birth weight infant (n=3), delivered a SGA infant (n=99)

^a . cigarette smoking in the first 6 months

^b . MVPA at the 1st phone interview (17–22 weeks)

TABLE 2

Lipoprotein particle concentrations^a and average particle size, by timing of blood draw. PIN Study, 2001–2005 (n=715).

	Full Term Deliveries				All Preterm Deliveries			
	<20 weeks		24–28 weeks		<20 weeks		24–28 weeks	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
LDL _{NMR}								
Total	1120.05	363.97	1374.57	464.84	1154.41	456.93	1328.50	497.20
IDL	38.73	46.16	81.46	70.97	38.67	49.29	73.97	74.87
Large	669.71	239.73	845.36	304.56	598.03	237.91	793.54	313.57
Medium	82.83	81.95	87.84	97.86	106.37	101.06	98.04	108.48
Small	328.77	321.69	359.89	395.71	411.32	394.15	362.93	411.22
HDL _{NMR}								
Total	32.78	5.30	33.30	5.62	33.65	5.95	34.02	6.66
Large	11.98	3.10	12.74	2.90	11.66	3.50	12.87	3.23
Medium	0.81	1.73	0.33	1.15	1.00	2.08	0.68	1.80
Small	19.98	4.51	20.23	4.90	20.98	5.18	20.46	5.63
VLDL _{NMR}								
Total	58.91	34.31	71.91	43.20	56.28	33.23	68.01	44.43
Large	1.54	2.28	2.87	3.25	2.22	3.70	3.53	4.70
Medium	27.52	20.53	34.52	23.52	27.60	19.35	32.74	23.82
Small	29.84	18.42	34.50	24.73	26.45	19.52	31.73	25.27
Average particle size								
LDL _{NMR}	21.85	0.74	21.92	0.75	21.66	0.86	21.89	0.82
HDL _{NMR}	9.70	0.37	9.77	0.37	9.64	0.40	9.76	0.40
VLDL _{NMR}	49.15	8.08	51.18	8.26	50.33	7.33	53.40	10.02
Total cholesterol	203.12	35.86	244.49	46.64	198.02	37.55	235.76	49.77
Triglycerides	121.05	51.01	166.63	64.76	131.55	70.72	175.28	82.15

Abbreviations: SD, standard deviation; LDL, low-density lipoprotein; IDL, intermediate-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein

^a. Concentrations were measured in particle nanomoles/L for (VLDL_{NMR} and HDL_{NMR}) and $\mu\text{moles/L}$ (for HDL_{NMR}), particle size was measured in nanometers.

TABLE 3

Adjusted hazard ratios^a for the association between lipids and gestational age at delivery for births <37 weeks, PIN Study, 2001–2005 (n=715).

	<20 weeks		24–28 weeks		Change from <20 to 24–28 weeks	
	HR	95% CI	HR	95% CI	HR	95% CI
LDL _{NMR}						
Total	1.04	(0.85,1.27)	0.86	(0.69,1.07)	0.76	(0.60,0.97)
IDL	0.95	(0.77,1.17)	0.84	(0.66,1.06)	0.84	(0.66,1.08)
Large	0.78	(0.64,0.96)	0.82	(0.66,1.01)	0.97	(0.77,1.23)
Medium	1.21	(1.00,1.45)	1.10	(0.90,1.34)	0.95	(0.76,1.20)
Small	1.18	(0.97,1.42)	0.99	(0.81,1.22)	0.82	(0.66,1.03)
HDL _{NMR}						
Total	1.18	(0.96,1.44)	1.06	(0.86,1.30)	0.90	(0.71,1.15)
Large	0.97	(0.79,1.18)	0.98	(0.80,1.21)	1.01	(0.79,1.29)
Medium ^b	1.16	(0.77,1.74)	1.90	(1.19,3.02)		
Small	1.19	(0.97,1.45)	1.00	(0.81,1.23)	0.80	(0.62,1.02)
VLDL _{NMR}						
Total	0.77	(0.61,0.98)	0.88	(0.70,1.12)	1.03	(0.81,1.30)
Large	1.19	(1.01,1.41)	1.15	(0.95,1.38)	1.05	(0.86,1.27)
Medium	0.82	(0.64,1.04)	0.87	(0.69,1.11)	0.93	(0.72,1.20)
Small	0.78	(0.62,0.98)	0.89	(0.71,1.11)	1.02	(0.82,1.28)
Average Particle Size LDL _{NMR}	0.84	(0.69,1.02)	0.94	(0.77,1.15)	1.11	(0.88,1.40)
Average Particle Size HDL _{NMR}	0.91	(0.75,1.11)	1.01	(0.82,1.24)	1.16	(0.92,1.47)
Average Particle Size VLDL _{NMR}	1.14	(0.96,1.36)	1.25	(1.03,1.51)	1.23	(0.98,1.55)

Abbreviations: HR, hazard ratio; CI, confidence interval, LDL, low-density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; VLDL, very low-density lipoprotein

^a . Adjusted for measured triglyceride concentration, measured total HDL concentration (LDL and VLDL models), measured total LDL concentration (HDL models), maternal age, race (white as reference), number of years of education, household income expressed as percentage of the federal poverty line, pre-pregnancy body mass index (normal weight as reference), and smoking.

^b . Medium HDL_{NMR} is categorized as any or no detectable concentration; the change in medium HDL_{NMR} from <20 to 24–28 weeks was not assessed.

NOTE: Bold font used to indicate statistically significant estimates (p<0.05)

Adjusted hazard ratios^a for the association between lipids and timing of delivery among spontaneous deliveries (<37 weeks) only

TABLE 4

	<20 weeks		24–28 weeks		Change from <20 to 24–28 weeks	
	HR	95% CI	HR	95% CI	HR	95% CI
LDL _{NMR}						
Total	0.93	(0.70,1.24)	0.67	(0.48,0.94)	0.59	(0.41,0.85)
IDL	0.89	(0.66,1.20)	0.68	(0.47,0.98)	0.69	(0.47,1.01)
Large	0.73	(0.55,0.97)	0.75	(0.56,1.00)	0.92	(0.67,1.27)
Medium	1.21	(0.95,1.56)	1.06	(0.80,1.40)	0.90	(0.65,1.23)
Small	1.11	(0.85,1.45)	0.86	(0.64,1.17)	0.72	(0.52,1.00)
HDL _{NMR}						
Total	1.14	(0.87,1.50)	1.14	(0.86,1.51)	1.07	(0.77,1.48)
Large	0.97	(0.74,1.27)	0.97	(0.73,1.29)	0.99	(0.70,1.39)
Medium ^b	1.09	(0.62,1.91)	1.94	(1.01,3.75)		
Small	1.16	(0.88,1.52)	1.08	(0.82,1.43)	0.96	(0.69,1.33)
VLDL _{NMR}						
Total	0.76	(0.55,1.04)	0.95	(0.70,1.29)	1.15	(0.84,1.57)
Large	1.16	(0.93,1.46)	1.12	(0.87,1.44)	1.05	(0.80,1.36)
Medium	0.84	(0.62,1.14)	0.96	(0.71,1.30)	1.04	(0.75,1.43)
Small	0.74	(0.54,1.00)	0.91	(0.67,1.23)	1.09	(0.81,1.47)
Average Particle Size LDL _{NMR}	0.85	(0.65,1.10)	0.99	(0.75,1.32)	1.19	(0.86,1.64)
Average Particle Size HDL _{NMR}	0.94	(0.72,1.23)	1.03	(0.78,1.36)	1.14	(0.82,1.58)
Average Particle Size VLDL _{NMR}	1.17	(0.93,1.47)	1.24	(0.95,1.62)	1.20	(0.87,1.67)

Abbreviations: HR, hazard ratio; CI, confidence interval, LDL, low-density lipoprotein; IDL, intermediate-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein

^a . Adjusted for measured triglyceride concentration, measured total HDL concentration (LDL and VLDL models), measured total LDL concentration (HDL models), maternal age, race (white as reference), number of years of education, household income expressed as percentage of the federal poverty line, pre-pregnancy body mass index (normal weight as reference), and smoking.

^b . Medium HDL_{NMR} is categorized as any or no detectable concentration; the change in medium HDL_{NMR} from <20 to 24–28 weeks was not assessed.

NOTE: Bold font used to indicate statistically significant estimates (p<0.05)