OBSTETRICS

Is maternal lipid profile in early pregnancy associated with pregnancy complications and blood pressure in pregnancy and long term postpartum?

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BACKGROUND: An atherogenic lipid profile is a risk factor for the initiation and progression of atherosclerosis. This ultimately leads to cardiovascular disease. Women with a history of hypertensive disorders of pregnancy are at increased risk of sustained hypertension and cardiovascular disease later in life. Currently it is unclear whether dyslipidemia during pregnancy contributes to these risks.

OBJECTIVE: The objective of the study was to determine the associations between early pregnancy maternal lipid profile, hypertensive disorders of pregnancy, and blood pressure during and years after pregnancy.

STUDY DESIGN: We included 5690 women from the Generation R Study, an ongoing population-based prospective birth cohort. Two hundred eighteen women (3.8%) developed gestational hypertension and 139 (2.4%) preeclampsia. A maternal lipid profile consisting of total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, remnant cholesterol, and non—high-density lipoprotein cholesterol was determined in early pregnancy (median, 13.4 weeks of gestation). Systolic and diastolic blood pressures were measured in early, mid-, and late pregnancy and 6 and 9 years after pregnancy.

RESULTS: Triglycerides and remnant cholesterol in early pregnancy were positively associated with preeclampsia. Maternal lipid levels in early pregnancy were not associated with gestational hypertension. Total cholesterol, low-density lipoprotein cholesterol, non—high-density lipoprotein cholesterol, and especially triglycerides and remnant cholesterol were positively associated with blood pressure in pregnancy and 6 and 9 years after pregnancy. Triglycerides and remnant cholesterol are positively associated with sustained hypertension 6 and 9 years after pregnancy.

CONCLUSION: An atherogenic lipid profile in early pregnancy reflecting impaired triglyceride-rich lipoprotein metabolism is independently associated with preeclampsia and blood pressure throughout pregnancy but also with sustained hypertension long term postpartum. Lipid levels in early pregnancy may help to identify women at risk for future hypertension and perhaps also women at risk for future cardiovascular disease.

Key words: atherosclerosis, lipoproteins, preeclampsia, pregnancy

Hypertensive disorders of pregnancy (HDP) affect 2—10% of pregnancies in the Western world. They are associated with an increased risk of morbidity and mortality for both mother and child.[1] Long term after pregnancy, these women remain at risk of hypertension, which makes them more susceptible for later-life cardiovascular disease (CVD).[2,3] Better understanding of the underlying risk factors of HDP and those of postpartum hypertension might help to identify women at risk of later-life CVD in an early stage.

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In pregnancy, adaptations of maternal lipid metabolism are needed for fetal growth and development. These adaptations include the development of maternal hyperlipidemia.[4] High levels of remnant cholesterol and an atherogenic lipid profile, defined by high levels of total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-c) and/or a low level of high-density lipoprotein cholesterol (HDL-c), are risk factors for the initiation and progression of atherosclerosis, ultimately leading to CVD.[5—9]

The early stage of atherosclerosis is characterized by the accumulation of foam cells (lipid-laden macrophages) in the arterial vessel wall.[5] Atherosis is a similar process, which is observed in the spiral arteries of the placenta in 20—40% of women with preeclampsia (PE).[3,10] The exact pathophysiology remains unclear but might be associated with an atherogenic lipid profile in early pregnancy.[11—13]

Our hypothesis is that an atherogenic lipid profile increases the risk of endothelial damage through oxidative stress mechanisms in the arterial vessel wall.[14,15] Dysfunctional endothelium can lead to gestational hypertension (GH) and/or prehypertension. Eventually this may result in sustained hypertension postpartum.[14—16] We hypothesize that women with an atherogenic lipid profile in early pregnancy are at increased risk of HDP and a higher blood pressure during and years after pregnancy.

In this study we aimed to assess the associations between maternal lipid profile in early pregnancy, HDP, blood pressure throughout pregnancy, and blood pressure and sustained hypertension 6 and 9 years after pregnancy.

Materials and Methods

Design and study population

This study was embedded in the Generation R Study, an ongoing

AJOG at a Glance

Why was this study conducted?

This study was conducted to evaluate whether an atherogenic lipid profile in early pregnancy contributes to the development of pregnancy complications and sustained hypertension later in life. This may contribute to cardiovascular disease later in life.

Key findings

Triglycerides and remnant cholesterol in early pregnancy are positively associated with preeclampsia. Total cholesterol, low-density lipoprotein cholesterol, non—high-density lipoprotein cholesterol, and especially triglycerides and remnant cholesterol are positively associated with blood pressure in pregnancy and 6 and 9 years after pregnancy. Triglycerides and remnant cholesterol are positively associated with sustained hypertension 6 and 9 years after pregnancy.

What does this add to what is known?

Lipid levels in early pregnancy are associated with a cardiovascular burden for the mother by increasing the risk of preeclampsia and sustained hypertension and may therefore be used as an early marker for later-life cardiovascular disease.

population-based prospective cohort study from early pregnancy onward[17] and was approved by the Medical Ethical Committee of the Erasmus Medical Center in Rotterdam, The Netherlands (MEC 198.782/2001/31). Written informed consent was obtained from all participants.

For the present study, we included 5690 women with a live-born singleton and available information on lipid measurements in early pregnancy. We excluded women with a twin pregnancy, gestational diabetes, diabetes mellitus, hypercholesterolemia, and those using medication for the regulation of glucose or cholesterol during study enrollment (Figure 1).

Maternal lipid levels in early pregnancy

Nonfasting blood samples were obtained in early pregnancy (13.4 weeks of gestation, 90% range [10.5; 17.2]) by trained research nurses to determine the levels of total cholesterol, triglycerides, and HDL-c. Details of processing procedures have been described previously.[18] Total cholesterol, triglycerides and HDL-c were analyzed using standard laboratory methods. Their mean interassay coefficients of variation for total cholesterol, triglycerides, and HDL-c were, respectively, 4.2%, 3.4%, and 2.8%. Levels of LDL-c were calculated using the Friedewald equation.[19] Non—HDL-c was calculated by subtracting HDL-c from the total cholesterol and remnant cholesterol as ([total cholesterol − LDL-c] − HDL-c).

Maternal anthropometrics

We obtained information on prepregnancy weight through questionnaires at study enrollment. Prepregnancy body mass index (BMI) (kilograms per square meter) was calculated. Maternal weight (kilograms) and height (centimeters) were measured in early, mid-, and late pregnancy and 6 and 9 years after pregnancy without shoes and heavy clothing after which BMI (kilograms per square meter) was calculated. Prepregnancy weight and weight measured at enrollment in early pregnancy were highly correlated (Pearson's correlation coefficient 0.95 [value of $P < .001$]),[20] and therefore, the prepregnancy weight was used in the analyses.

Blood pressure and hypertensive disorders of pregnancy

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in early pregnancy (13.4 weeks of gestation, 90% range [10.5; 17.2 weeks]), midpregnancy (20.4 weeks of gestation, 90% range [19.1; 22.5]), late pregnancy (30.2 weeks of gestation, 90% range [29.0; 31.9]), and 6 years after pregnancy (6.0 years, 90% range [5.7; 7.3]) using a validated Omron 907 automated digital oscillometric sphygmomanometer (OMRON Healthcare Europe BV, Hoofddorp, The Netherlands).[21]

Nine years after pregnancy (9.7 years, 90% range [9.5; 10.4]), blood pressure was measured with the validated automatic sphygmomanometer Datascope Accutorr Plus (Paramus, NJ).[22] Blood pressure was measured 2 times over a 60 second interval, and the mean value was used for analyses.[23]

Information on HDP was obtained from medical records filled in by midwives or obstetricians and cross-checked with original hospital charts.[24] GH was defined as development of a SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg without proteinuria after 20 weeks of gestation in previous normotensive women.[25] PE was defined as the development of SBP ≥140 mm Hg and/or DBP ≥ 90 mm Hg with new-onset proteinuria in a random urine sample with no evidence of an urinary tract infection.[25]

Sustained hypertension at 6 and/or 9 years follow-up was defined when women had the diagnosis of hypertension filled in by questionnaires or if they used antihypertensive medication or if they had a mean SBP ≥140 mm Hg and/or a DBP ≥90 mm Hg during their visit at the research center.

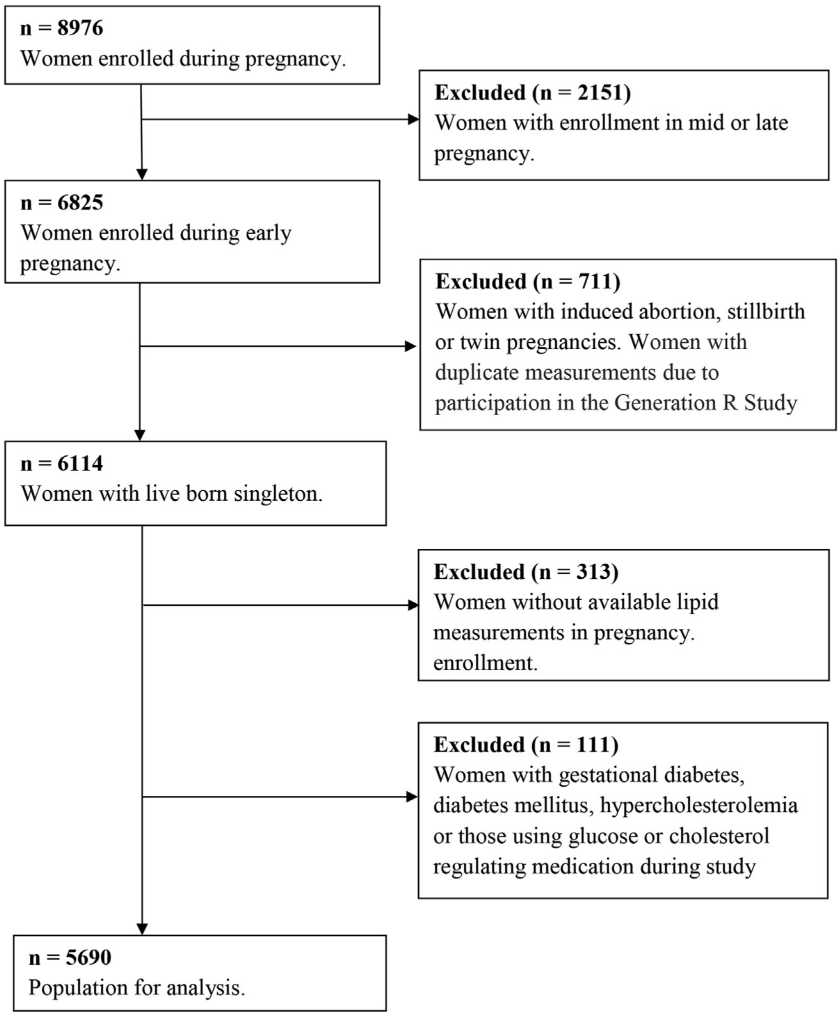
Covariates

Information on maternal age, ethnicity, educational level, and parity at intake was obtained through questionnaires. Information on gestational age at birth, child's sex, and birthweight was obtained from midwife and hospital registries.

Statistical analyses

A nonresponse analysis was conducted by comparing the characteristics of women included in this study (n = 5690) with women with inclusion in mid- or late pregnancy (n = 2151) (Supplemental Table). Missing data of the covariates were imputed using multiple imputations.[26]

FIGURE 1
Flowchart



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We investigated the association of maternal lipid levels in early pregnancy with HDP, blood pressure, and sustained hypertension using regression analyses. Potential confounders were selected based on their association with the outcome of interest and/or based on previous studies. Maternal glucose, smoking and alcohol use, and sex and birthweight of the child were considered as potential confounder but not selected in the final models because adding these variables did not improve the models.

The basic regression model adjusted for maternal age at enrollment and gestational age at the time of blood sampling. For blood pressure years after pregnancy, the basic model additionally adjusted for time since index pregnancy. The confounder model additionally adjusted for ethnicity, education, and parity. In a separate BMI model, we additionally adjusted for prepregnancy BMI. A value of $P < .05$ was considered statistically significant. IBM Statistical Package of Social Sciences version 24.0 for Windows (SPSS Inc, Chicago, IL) was used for all statistical analyses.

Results

We included 5690 women; 5333 women (93.7%) had a normotensive pregnancy, 218 (3.8%) developed GH, and 139 (2.4%) developed PE. Women were on average 29.5 (±5.1) years of age, 2358 women (41.4%) had a non-European ethnicity and the median pre-pregnancy BMI was 22.5 kg/m^2 (90% range, 18.6; 32.0) (Table 1). Lipid levels of women in our study are within the 25th and 75th age-specific percentiles of nonpregnant women participating in the Dutch Lifelines cohort study.[27] Changes in gestational lipid level per gestational age are presented in the Supplemental Figure.

Women with PE had significantly higher levels of triglycerides and remnant cholesterol compared with women with a normotensive pregnancy ($P < .05$). Other lipid levels were similar between the groups. Table 2 shows the distribution of maternal lipid levels in early pregnancy of women with a normotensive pregnancy, GH, PE, and sustained hypertension.

Table 3 shows the association between maternal lipid levels in early pregnancy and GH and PE. Women with higher levels of triglycerides were more at risk of developing PE (odds ratio [OR], 1.50, 95% CI [1.12; 2.01]). This association remained statistically significant after adjustment for confounders and pre-pregnancy BMI.

Women with higher levels of remnant cholesterol in early pregnancy were also more at risk of PE (OR, 2.13, 95% CI [1.08; 4.21]). After adjustment for pre-pregnancy BMI, this association was no longer significant. Total cholesterol, LDL-c, HDL-c, and non−HDL-c levels in early pregnancy were not associated with the risk of PE.

Additionally, we observed no association between any lipid level in early pregnancy and the risk of GH. All lipid levels, except HDL-c, were positively associated with blood pressure throughout pregnancy independent of prepregnancy BMI. HDL-c was only positively associated with blood pressure in early pregnancy (Figure 2).

Women with higher levels of triglycerides and remnant cholesterol in early pregnancy had a higher SBP 6 years after pregnancy. Total cholesterol, triglycerides, remnant cholesterol, and non–HDL-c levels were positively and independently associated with DBP 6 years after pregnancy (Figure 2). Nine years after pregnancy, women with higher levels of triglycerides and remnant cholesterol and lower levels of HDL-c in early pregnancy had a higher SBP. Nine years after pregnancy, triglycerides, remnant cholesterol, and non–HDL-c levels were positively associated and HDL-c levels were negatively and independently associated with DBP (Figure 2). Stratification for HDP did not influence these results (data not shown). Women with higher levels of triglycerides and remnant cholesterol were more at risk of developing sustained hypertension 6 and 9 years after pregnancy (Table 4).

Comment

This study shows that a lipid profile in early pregnancy that is characterized by higher levels of triglycerides and remnant cholesterol is associated with a higher blood pressure during pregnancy as well as a higher blood pressure and sustained hypertension 6 and 9 years afterward.

This atherogenic lipid profile is also associated with an increased risk of PE. Because blood pressure is an important risk factor for CVD, we hypothesize that women with increased lipid levels in early pregnancy are at risk of CVD later in life.[28,29] Therefore, the lipid level assessment in early pregnancy may be a tool to detect women at risk of high blood pressure and consequently women with a future risk of sustained hypertension.

Previous studies assessing the association between lipid levels in mid- and late pregnancy and HDP found a similar association between an increased risk of PE and specifically triglyceride but not total cholesterol levels.[11-13,30,31]

Triglycerides and remnant cholesterol levels reflect an impaired metabolism of triglyceride-rich lipoproteins such as very low-density lipoproteins and chylomicrons and their remnants, which are controlled by multiple pathways including lipoprotein lipase activity, which is associated with insulin sensitivity and free fatty acid composition as well as lipoprotein lipase–regulating enzymes such as apolipoprotein A5, apolipoprotein C3, and glycosylphosphatidylinositol-anchored high-density lipoprotein–binding protein 1.

Although the exact pathophysiology of PE remains to be elucidated, the current hypothesis is that symptoms of PE are caused by endothelial dysfunction related to hypoxia in the placenta.[3,14]

TABLE 1
Baseline characteristics (n = 5690)

Outcomes	Women
Pregnancy characteristics	
Age mother at enrollment, mean (SD), y	29.5 (5.1)
Gestational age at blood sampling, median (90% range), wks	13.4 (10.5; 17.2)
Non-European ethnicity, n, %	2358 (41.4)
Turkish	499 (21.2)
Surinamese	498 (21.1)
Moroccan	365 (15.5)
Cape Verdian	243 (10.3)
Dutch Antilles	185 (7.8)
Indonesian	162 (6.9)
Others	406 (17.2)
Lower education, n, %	656 (11.5)
Prepregnancy BMI, median (90% range), kg/m^2	22.5 (18.6; 32.0)
Systolic blood pressure at enrollment, mean (SD), mm Hg	115.6 (12.3)
Diastolic blood pressure at enrollment, mean (SD), mm Hg	68.3 (9.5)
Nulliparous, n, %	3489 (61.3)
Gestational hypertension, n, %	218 (3.8)
Preeclampsia, n, %	139 (2.4)
Gestational age at birth, median (90% range), wks	40.1 (36.9; 42.1)
Boy, n, %	2873 (50.5)
Birthweight, mean (SD), g	3401 (560)
Six years after pregnancy	
Time since index pregnancy, median (90% range), y	6.0 (5.7; 7.3)
Systolic blood pressure, mean (SD), mm Hg	119.0 (12.6)
Diastolic blood pressure, mean (SD), mm Hg	70.6 (9.8)
Sustained hypertension, n, %	325 (5.7)
Nine years after pregnancy	
Time since index pregnancy, median (90% range), y	9.7 (9.5; 10.4)
Systolic blood pressure, mean (SD), mm Hg	114.4 (12.5)
Diastolic blood pressure, mean (SD), mm Hg	68.4 (8.2)
Sustained hypertension, n, %	204 (3.6)
Other HDP than index pregnancy, n, %	155 (2.7)

Values are valid percentages for categorical variables, means (SD) for continuous variables with a normal distribution or medians (90% range) for continuous variables with a skewed distribution. Confounders were imputed.

BMI, body mass index; *HDP*, hypertensive disorders of pregnancy.

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TABLE 2
Maternal lipid profile in early pregnancy and maternal weight

Variables	Normotensive pregnancy (n = 5333)	Gestational hypertension[a] (n = 218)	Preeclampsia[b] (n = 139)	Sustained hypertension 6 years after pregnancy[c] (n = 325)	Sustained hypertension 9 years after pregnancy[d] (n = 204)
Lipid levels					
Gestational age at blood sampling, median (90% range), wks	13.4 (10.5; 17.2)[a]	12.9 (9.9; 16.8)	13.4 (10.5; 17.2)	13.5 (10.8; 17.2)	13.5 (10.3; 17.2)
Total cholesterol, mean (SD), mmol/L	4.81 (0.86)[c]	4.90 (0.90)	4.87 (0.87)	4.98 (0.87)	4.88 (0.89)
Triglycerides, median (90% range), mmol/L	1.26 (0.71; 2.34)[b,c,d]	1.32 (0.73; 2.27)	1.34 (0.82; 2.60)	1.43 (0.76; 2.78)	1.42 (0.79; 2.90)
LDL-c, mean (SD), mmol/L	2.42 (0.71)[c]	2.48 (0.71)	2.44 (0.73)	2.52 (0.73)	2.45 (0.71)
HDL-c, mean (SD), mmol/L	1.77 (0.35)[d]	1.79 (0.36)	1.77 (0.34)	1.76 (0.38)	1.73 (0.38)
Remnant cholesterol, median (90% range), mmol/L	0.57 (0.32; 1.06)[b,c,d]	0.60 (0.33; 1.03)	0.61 (0.37; 1.16)	0.65 (0.34; 1.23)	0.65 (0.36; 1.32)
Non-HDL-c, mean (SD), mmol/L	3.03 (0.82)[c,d]	3.10 (0.81)	3.10 (0.83)	3.23 (0.85)	3.16 (0.82)
Weight					
Prepregnancy BMI, median (90% range), kg/m^2	22.5 (18.6; 31.6)[a,b,c,d]	24.7 (19.3; 35.9)	23.8 (18.8; 35.4)	25.3 (19.6; 35.8)	25.8 (19.8; 36.7)
Weight gain in pregnancy, mean (SD), kg	15.1 (5.8)[a]	16.9 (6.4)	16.6 (7.1)	14.3 (6.2)	14.3 (5.6)
BMI 6 years after pregnancy, median (90% range), kg/m^2	24.5 (19.7; 35.0)[a,b,c,d]	26.7 (20.7; 41.9)	27.5 (19.8; 41.9)	28.0 (21.1; 40.7)	30.5 (21.6; 42.7)
BMI 9 years after pregnancy, median (90% range), kg/m^2	24.6 (19.9; 35.6)[a,b,c,d]	27.0 (20.7; 39.2)	27.6 (20.0; 39.3)	28.4 (21.3; 41.2)	31.2 (21.5; 44.2)

Values are means (SD) for continuous variables with a normal distribution or medians (90% range) for continuous variables with a skewed distribution. Presented values are not imputed. Differences between individual groups, indicated as superscript letters a, b, c, and d, were tested through a Student *t* test.

BMI, body mass index; *HDL-c*, high-density lipoprotein cholesterol; *LDL-c*, low-density lipoprotein cholesterol.

[a,b,c,d] Student *t* test value of $P < .05$ between women with gestational hypertension (a); preeclampsia (b); sustained hypertension 6 years after pregnancy (c); sustained hypertension 9 years after pregnancy (d) and women with a normotensive pregnancy.

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TABLE 3
Associations of maternal lipid profile in early pregnancy with gestational hypertension and preeclampsia

Variables	Normotensive pregnancy (n = 5333)	Gestational hypertension, OR (95% CI) (n = 218)	*P*-value	Preeclampsia, OR (95% CI) (n = 139)	*P* value
Total-cholesterol, mmol/L					
Basic model	Reference	1.21 (1.11; 1.32)	.01	1.07 (0.88; 1.32)	.49
Confounder model	Reference	1.17 (0.99; 1.38)	.06	1.06 (0.86; 1.30)	.60
BMI model	Reference	1.10 (0.93; 1.30)	.29	1.01 (0.82; 1.24)	.95
Triglycerides, mmol/L					
Basic model	Reference	1.13 (0.87; 1.47)	.37	1.47 (1.10; 1.96)	.01
Confounder model	Reference	1.22 (0.93; 1.60)	.15	1.50 (1.12; 2.01)	.01
BMI model	Reference	1.02 (0.77; 1.36)	.87	1.37 (1.01; 1.85)	.04
LDL-c, mmol/L					
Basic model	Reference	1.19 (1.06; 1.34)	.37	1.03 (0.80; 1.31)	.85
Confounder model	Reference	1.18 (0.97; 1.43)	.11	1.02 (0.80; 1.30)	.90
BMI model	Reference	1.06 (0.86; 1.29)	.60	0.94 (0.73; 1.20)	.61
HDL-c, mmol/L					
Basic model	Reference	1.24 (1.01; 1.52)	.43	0.97 (0.75; 1.27)	.97
Confounder model	Reference	1.01 (0.67; 1.52)	.98	0.91 (0.55; 1.50)	.70
BMI model	Reference	1.30 (0.85; 1.98)	.23	1.07 (0.64; 1.79)	.79
Remnant cholesterol, mmol/L					
Basic model	Reference	1.33 (0.75; 2.38)	.33	2.09 (1.08; 4.06)	.03
Confounder model	Reference	1.57 (0.86; 2.85)	.14	2.13 (1.08; 4.21)	.03
BMI model	Reference	1.06 (0.57; 1.99)	.85	1.72 (0.85; 3.45)	.13
Non-HDL-c, mmol/L					
Basic model	Reference	1.18 (1.09; 1.28)	.22	1.10 (0.89; 1.35)	.38
Confounder model	Reference	1.18 (1.00; 1.41)	.05	1.09 (0.88; 1.35)	.42
BMI model	Reference	1.05 (0.88; 1.26)	.56	1.00 (0.81; 1.25)	.97

Values are odds ratios (95% confidence interval). The basic model was adjusted for maternal age at intake and gestational age at blood sampling. The confounder model was basic model additionally adjusted for ethnicity, educational level, and parity. The BMI model was confounder model additionally adjusted for prepregnancy BMI.

BMI, body mass index; *CI*, confidence interval; *HDL-c*, high-density lipoprotein cholesterol; *LDL-c*, low-density lipoprotein cholesterol; *OR*, odds ratio.

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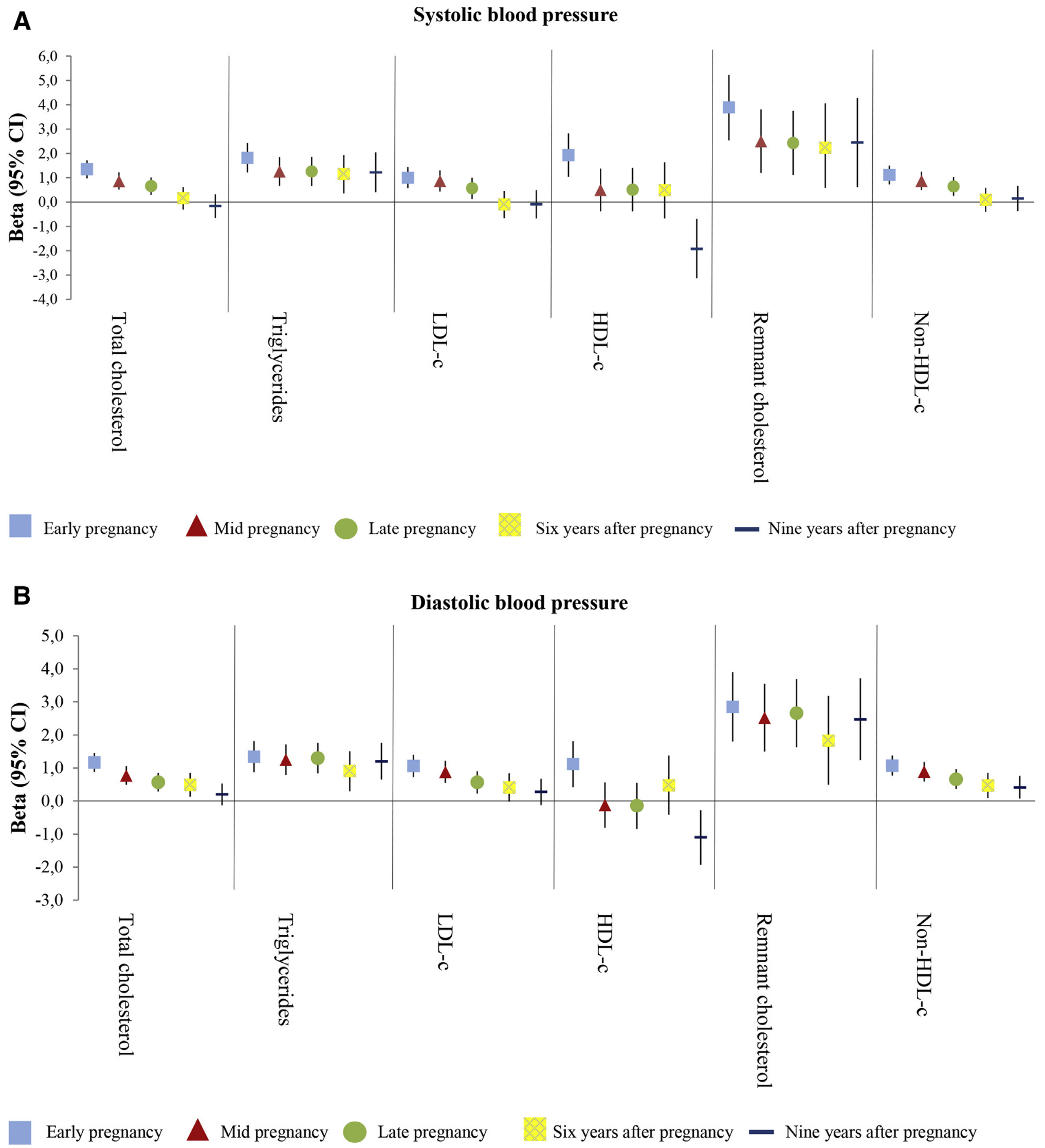
This placental hypoxia results in local inflammation and oxidative stress accompanied by acute atherosis of the spiral arteries of the placenta.[32,33] In general, atherosis is thought to be a result of accumulation of cholesterol-rich particles such as LDL-c; however, it can also be caused by triglyceride-rich particles.[15,34,35]

Additionally, recent studies found that women with PE had a significant increase of adipocyte fatty acid–binding proteins (AFABP), which are intracellular lipid chaperones that coordinate lipid responses in cells and are also strongly linked to metabolic and inflammatory pathways.[36,37] When elevated, AFABP is associated with increased levels of triglycerides. On the other hand, a reduced expression of these AFABPs leads to decreased levels of triglycerides and also a reduced risk of CVD.[38,39] This supports the suggested involvement of triglyceride-rich lipoproteins in the pathogenesis of PE but also shows that triglyceride-rich lipoproteins might contribute to the risk of CVD in PE. This may explain the association between triglyceride levels in early pregnancy and PE.

In contrast to previous studies, we observed no association of maternal lipid levels in early pregnancy with GH.[40,41] Our finding might be explained by the difference in the pathophysiology between GH and PE. GH is often found in women with an unfavorable metabolic profile (eg, obesity, diabetes)[42,43] in contrast to PE, which is believed to be partially caused by a genetic component.[44-47]

To measure the possible impact of the metabolic profile, we corrected our analyses for maternal BMI and found no association of the maternal lipid profile with GH. Additionally we observed no

FIGURE 2
Association of maternal lipid profile with blood pressure



A, Association of maternal lipid profile in early pregnancy with systolic blood pressure. Data were adjusted for maternal age at intake, gestational age at blood sampling, time since index pregnancy, ethnicity, educational level, and parity and prepregnancy BMI. Values are linear regression coefficients (95% confidence interval). **B,** Association of maternal lipid profile in early pregnancy with diastolic blood pressure. Data were adjusted for maternal age at intake, gestational age at blood sampling, time since index pregnancy, ethnicity, educational level, and parity and prepregnancy BMI. Values are linear regression coefficients (95% confidence interval).

BMI, body mass index; *CI*, confidence interval; *HDL-c*, high-density lipoprotein cholesterol; *LDL-c*, low-density lipoprotein cholesterol.

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TABLE 4
Associations of maternal lipid profile in early pregnancy with sustained hypertension years after pregnancy

Variables	Normotensive pregnancy (n = 5333)	Six years after Pregnancy, OR (95% CI) (n = 325)	*P* value	Nine years after Pregnancy, OR (95% CI) (n = 204)	*P* value
Total cholesterol, mmol/L	Reference	1.13 (0.98; 1.30)	.09	0.92 (0.77; 1.10)	.37
Triglycerides, mmol/L	Reference	1.56 (1.27; 1.91)	< .001	1.53 (1.19; 1.97)	.001
LDL-c, mmol/L	Reference	1.06 (0.90; 1.25)	.50	0.84 (0.68; 1.04)	.12
HDL-c, mmol/L	Reference	0.98 (0.69; 1.39)	.90	0.79 (0.51; 1.24)	.31
Remnant cholesterol, mmol/L	Reference	2.46 (1.55; 3.90)	< .001	2.46 (1.39; 4.33)	.002
Non-HDL-c, mmol/L	Reference	1.15 (1.00; 1.33)	.05	0.96 (0.80; 1.15)	.65

Values are odds ratios (95% confidence interval). Adjusted for maternal age at intake, interval time, gestational age at blood sampling, ethnicity, educational level, parity, and maternal body mass index.

CI, confidence interval; *HDL-c*, high-density lipoprotein cholesterol; *LDL-c*, low-density lipoprotein cholesterol; *OR*, odds ratio.

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association of maternal lipid levels in early pregnancy with blood pressure for women with GH (data not shown). This might be explained by the small sample size of women with GH with both blood pressure and lipid level measurements, which could contribute to our finding of no association between triglycerides and GH. However, it might also be possible that different laboratory methods between studies explain the disparity of maternal lipid levels in early pregnancy with GH.

In pregnancy, plasma HDL-c concentrations start to rise at 10 weeks of gestation, peaking at 20 weeks. The initial rise in plasma HDL-c occurs around the time of the establishment of the fetoplacental circulation generating oxidative stress. It is thought that HDL-c increases to protect the maternal vascular endothelium and that this rise does not occur properly in women with PE.[48]

In this study, we found no difference in HDL-c levels between normotensive women and women with PE (Table 2). This may be due to the small number of women with PE in our study. The positive association between HDL-c and early pregnancy blood pressure was unexpected. However, a previous study suggested that this association might be explained by circulating endothelial progenitor cells such as CD34-positive cells.[49] In individuals with high, but not with low, levels of circulating CD34-positive cells, HDL was found to be positively associated with hypertension. The association of HDL-c levels and hypertension is also described previously in men and nonpregnant women.[50]

BMI in nonpregnant adults is associated with an increased risk of an atherogenic lipid profile.[51-53] Adjustment for BMI in our analyses attenuated the observed associations of early pregnancy maternal lipid levels with HDP and blood pressure. Additionally, BMI is associated with HDP and increased SBP and DBP in pregnancy.[28,54] Although BMI has been previously associated with an increased risk of CVD through insulin resistance, inflammatory cytokines, and hypertension, the exact underlying mechanisms remain unclear.[55-57]

We hypothesize that a higher prepregnancy BMI leads to altered lipid levels in early pregnancy because of oxidative-modified lipoproteins, leading to endothelial dysfunction and an increased risk of HDP.[5] We considered excessive weight gain during pregnancy as a potential confounder in the association between lipid levels and PE because obesity may lead to higher lipid levels during pregnancy.[53,58] However, regression analyses in our study showed similar results after adjusting for excessive weight gain in pregnancy or prepregnancy BMI, which is in agreement with previous studies showing that excessive weight gain during pregnancy, as defined by the 2009 Institute of Medicine guidelines, is not associated with higher lipid levels, whereas prepregnancy obesity does.[53,58,59]

We additionally adjusted our analyses for glucose because a higher BMI is linked to insulin resistance and therefore to lipid accumulation.[60] The associations of lipid levels in early pregnancy with HDP and blood pressure remained significant after correction for glucose. Our results show a positive association of maternal lipid levels in early pregnancy with SBP and DBP throughout pregnancy and 6 and 9 years after pregnancy, independently of maternal BMI.

These findings are in agreement with a previous study describing that both the maternal lipid profile and BMI independently influence SBP and DBP.[61] We found that especially triglycerides contribute to SBP and DBP. Triglyceride-rich lipoproteins can cause atherosclerosis of the vascular system and endothelial damage via oxidative mechanisms.[15,34,62,63] Possibly this may result in impaired release of nitric oxide and lead to insufficient nitric oxide—dependent vasodilatation resulting in hypertension.[64,65]

Strengths and limitations

The strength of our study is that we are the first to assess non—HDL-c and remnant cholesterol measures, which are new important risk factors for CVD and may therefore be used as a clinical tool to predict a HDP and future CVD.[66,67]

On the other hand, some limitations need to be considered. First, venous blood samples were obtained in a nonfasting state. According to the joint consensus statement from the European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine, lipids and lipoproteins change minimally in response to normal food intake.[68,69] It is stated that only if nonfasting plasma triglycerides are >5 mmol/L, a fasting blood sample could be considered.[68] In our study, triglycerides did not exceed 5 mmol/L and only 7 patients had triglycerides >4 mmol/L. Excluding these patients from our analyses did not affect our results.

Second, prepregnancy BMI was self-reported. Nevertheless, prepregnancy BMI was strongly correlated with BMI measured in early pregnancy (Pearson's correlation coefficient, r 0.95 [$P<.001$]), which makes misclassification unlikely.

Third, other obesity indices as waist-hip ratio and waist circumference are also suggested to define cardiovascular risk.[70] In our study population, waist circumference was measured only 9 years after pregnancy. However, after correcting blood pressure measurements 9 years after pregnancy for waist circumference, the results remained the same (data not shown).

Fourth, the observational nature of this study does not allow for inference of causality and does not preclude the existence of residual confounding.

Fifth, blood samples were obtained in early pregnancy, whereas dyslipidemia is more profound in mid- and late pregnancy.[71]

Sixth, levels of total cholesterol, triglycerides, LDL-c, remnant cholesterol, and non-HDL-c are higher in overweight women (BMI 25–30 kg/m^2) compared with normal-weight women and even higher in obese women (BMI >30 kg/m^2). Analyses were not stratified by BMI at intake because the results did not differ between obese and normal-weight women.

Finally, our results might not be generalizable to all women because of the selection of a relatively healthy population, which may explain the number of HDP (Supplemental Table).

Conclusion

In conclusion, maternal lipid levels in early pregnancy are associated with blood pressure throughout pregnancy and years after pregnancy. Moreover, higher levels of triglycerides and remnant cholesterol in early pregnancy are associated with an increased risk of PE and sustained hypertension long term postpartum. Therefore, maternal lipid levels in early pregnancy are associated with a cardiovascular burden for the mother by increasing the risk of PE and sustained hypertension and may therefore be used as an early marker for later-life CVD. ■

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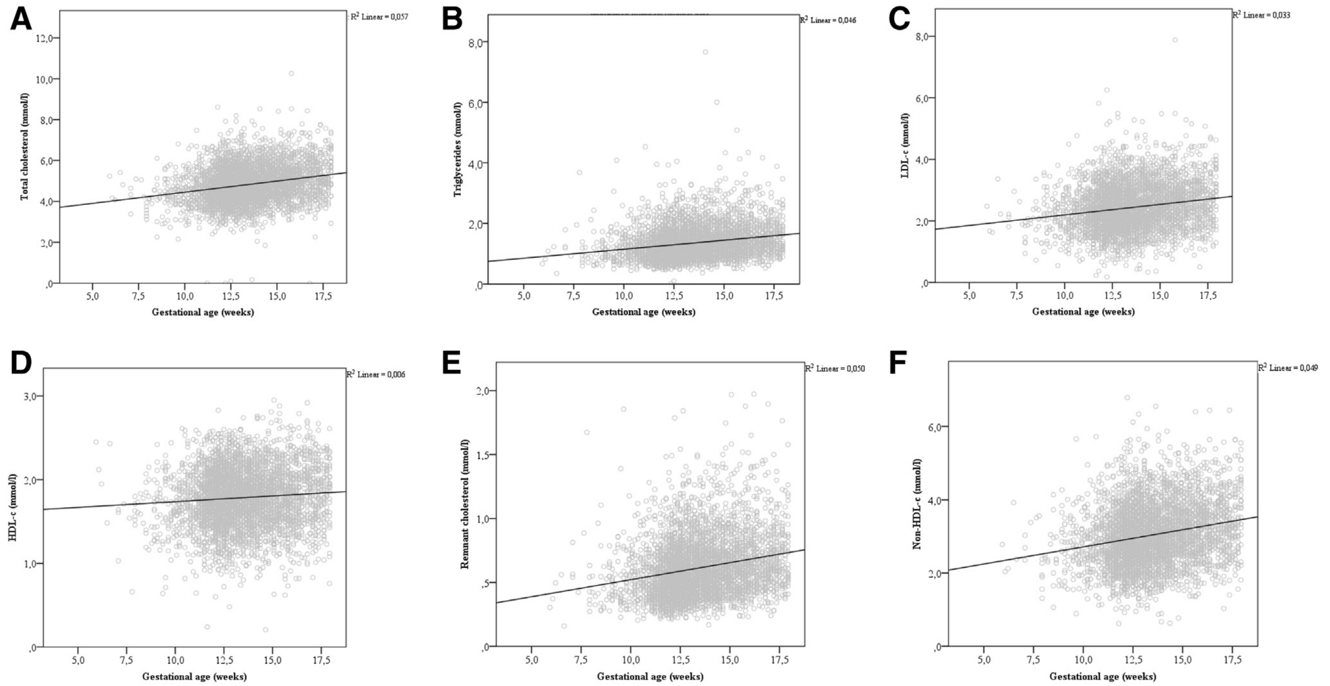
SUPPLEMENTAL FIGURE

Scatterplot of lipid levels in early pregnancy



Graphs represent changes in gestational lipid level per gestational age (weeks).

A, Total cholesterol. **B,** Triglycerides. **C,** LDL-cholesterol. **D,** HDL-cholesterol. **E,** Remnant cholesterol. **F,** Non—HDL-cholesterol.

HDL-c, high-density lipoprotein cholesterol; *LDL-c*, low-density lipoprotein cholesterol.

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SUPPLEMENTAL TABLE 1

Baseline characteristics between women with available lipid measurements and without available lipid measurements

Outcomes	Lipid measurements available (n = 5690)	No lipid measurements available (n = 2151)	*P* value
Maternal characteristics in pregnancy			
Age of mother at enrollment, mean (SD), y	29.5 (5.1)	29.5 (6.0)	.68
Non-European ethnicity, n, %	2358 (41.4)	1077 (55.9)	< .001
Lower education, n, %	656 (11.5)	324 (17.8)	< .001
Prepregnancy BMI, median (90% range), kg/m^2	22.5 (18.6; 32.0)	22.8 (18.3; 33.5)	.002
Midpregnancy BMI, median (90% range), kg/m^2	24.7 (20.3; 33.9)	24.9 (19.9; 35.2)	.005
SBP at enrollment, mean (SD), mm Hg	115.6 (12.3)	114.6 (11.9)	.001
DBP at enrollment, mean (SD), mm Hg	68.3 (9.5)	66.7 (9.4)	< .001
Nulliparous, n, %	3489 (61.3)	1037 (49.5)	< .001
Gestational hypertension, n, %	218 (3.8)	59 (3.0)	.03
Preeclampsia, n, %	139 (2.4)	49 (2.5)	.71
Gestational age at birth, median (90% range), wks	40.1 (36.9; 42.1)	40.0 (36.3; 42.1)	< .001
Boy, n, %	2873 (50.5)	1071 (50.5)	.99
Birthweight, mean (SD), g	3401 (560)	3377 (570)	.10

Values are valid percentages for categorical variables, means (SD) for continuous variables with a normal distribution, or medians (90% range) for continuous variables with a skewed distribution. Confounders were imputed.

BMI, body mass index; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure.

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