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Associations of maternal metabolic profile with placental and fetal cerebral and cardiac hemodynamics

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ABSTRACT

Objective: Maternal obesity and metabolic health affect pregnancy outcomes. We examined whether maternal metabolic profiles are associated with placental and fetal hemodynamics.
Study Design: In a population-based prospective cohort study among 1175 women we examined the associations of an adverse maternal metabolic profile in early pregnancy with placental, fetal cerebral and cardiac hemodynamic development. We obtained maternal pre-pregnancy BMI by questionnaire and measured blood pressure, cholesterol, triglycerides and glucose concentrations at a median gestational age of 12.6 (95 % range 9.6–17.1) weeks. An adverse maternal metabolic profile was defined as ≥4 risk factors. Placental and fetal hemodynamics were measured by pulsed-wave-Doppler at a median gestational age of 30.3 (95 % range 28.8–32.3) weeks.
Results: An adverse maternal metabolic profile was associated with a 0.29 Z-score higher (95 %CI 0.08−0.50) fetal cerebral middle artery pulsatility index (PI), but not with placental or fetal cardiac hemodynamic patterns. When the individual components of an adverse maternal metabolic profile were assessed, we observed that higher maternal total cholesterol and triglyceride concentrations were associated with a higher cerebral middle artery PI (Z-score, 0.09 (95 %CI 0.02−0.15), 0.09 (95 %CI 0.03−0.15) per Z-score increase). Higher total and HDL maternal cholesterol concentrations were also associated with a higher aorta ascendens peak systolic velocity (PSV) Z-score, 0.08 (95 %CI 0.01−0.14)), and a larger left cardiac output (Z-score, 0.08 (95 %CI 0.00−0.15), respectively).
Conclusion: An adverse maternal metabolic profile, especially higher cholesterol and triglycerides concentrations, are associated with increased fetal cerebral vascular resistance and larger fetal aorta ascendens diameter, PSV and left cardiac output, but not with placental vascular resistance indices. Further studies are needed to identify long-term consequences of the observed associations.

Introduction

Maternal pre-pregnancy obesity is strongly related to metabolic disturbances during pregnancy, including insulin resistance, an adverse cholesterol profile and high triglycerides concentrations [1,2]. Both maternal pre-pregnancy obesity and these subsequent metabolic disturbances are major risk factors for pregnancy complications and adverse cardiovascular outcomes in offspring [3]. The mechanisms by which maternal pre-pregnancy obesity leads to adverse fetal and childhood outcomes might involve suboptimal early placental development leading to placental and fetal hemodynamic alterations [4].

Several studies have shown that maternal pre-pregnancy obesity, gestational diabetes and hyperlipidemia are associated with larger placental weight at birth [5–7]. An adverse maternal metabolic profile may also lead to a pro-inflammatory state leading to reduced placental vascularization, placental infarction and reduced placenta growth [8]. Placental weight is only a crude measure of placental development and function during pregnancy. Utero-placental and feto-placental peripheral vascular resistance can be assessed by Doppler ultrasound of the uterine and umbilical arteries throughout pregnancy. Altered vascular resistance in the main placental arteries may subsequently lead to changes in blood circulation of the brain and heart of the fetus.

We hypothesized that an adverse maternal early-pregnancy metabolic profile affects early placental development leading to subsequent adaptations in the placental, fetal cerebral and cardiac circulation. We examined in a population-based prospective cohort study among 1175 mothers and their children, the

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associations of maternal early pregnancy metabolic profile and its separate components with placental, fetal cerebral and cardiac hemodynamics.

Methods

Design and study population

This study was embedded in the Generation R Study, a population-based, prospective cohort study from fetal life onwards in Rotterdam, the Netherlands [9,10]. The Medical Ethics Committee of the Erasmus MC, University Medical Center, Rotterdam, had approved the study (2001). All children were born between April 2002 and January 2006. Detailed assessments of fetal and childhood growth and development were conducted in a random subgroup of 1232 Dutch mothers and children [11]. For the current analyses, twin pregnancies (n = 15), and pregnancies leading to perinatal death (n = 2) were excluded from this analyses, resulting in 1215 singleton live born children. First trimester maternal metabolic profile measurements and third trimester placental and fetal hemodynamic patterns were available in 1175 mothers and their children (Fig. 1).

Maternal metabolic profile

At enrollment, we measured maternal height (cm) without shoes and clothing. Information about maternal weight just before pregnancy was obtained by questionnaire. We calculated BMI (kg/m^2). First trimester blood pressure and blood samples were collected at a median gestational age of 12.6 (95 % range 9.6–17.1) weeks, as described in detail [12,13]. Briefly, blood pressure measurements were performed when participants were seated in upright position with back support and were asked to relax for 5 min. A cuff was placed around the non-dominant upper arm, which was supported at the level of the heart, with the bladder midline over the brachial artery pulsation. In case of an upper arm exceeding 33 cm, a larger cuff (32–42 cm) was used. The mean value of two BP readings over a 60-second interval was documented for each participant [14,15]. All non-fasting blood samples were transported to a dedicated laboratory facility in Rotterdam, the Netherlands (STAR-MDC). Processing was aimed to finish within a maximum of 3 h after sampling and stored at −80 °C. Total cholesterol, HDL-cholesterol, triglycerides and glucose concentrations are enzymatic assays and were measured with c702 module on the Cobas 8000 analyzer [13]. As a measure of a metabolic syndrome like phenotype, we defined an adverse maternal metabolic profile as ≥ 4 of the following risk factors; BMI higher than 25.0, blood pressure, total cholesterol, triglycerides and glucose concentrations belonging to the highest 25 % of our study population or HDL-cholesterol concentrations belonging to the lowest 25 % of our study population (16).

Third trimester placental and fetal hemodynamic characteristics

Utero-placental and feto-placental peripheral vascular resistance were assessed by pulsed-wave Doppler at a median gestational age of 30.3 (95 % range 28.8–32.3) weeks, as described previously [17,18].

Uterine artery resistance index (RI) was measured in the uterine arteries near the crossover with the external iliac artery. Umbilical artery pulsatility index (PI) was determined in a free-floating loop of the umbilical cord. A higher uterine RI and umbilical artery PI indicated a higher peripheral vascular resistance [19,20]. Middle cerebral artery Doppler measurements were obtained in the proximal part of the cerebral arteries. The middle cerebral artery PI quantifies the redistribution of blood flow, and when lower, in favor of the fetal brain. Reductions in middle cerebral artery PI is a valid indicator of fetal circulatory redistribution [21,22]. An indicator of the 'brain-sparing effect' is a raised ratio between the umbilical artery PI and the cerebral artery PI (U/C ratio) [23]. Cardiac flow-velocity waveforms at the level of the mitral valves were recorded from the apical 4-chamber view of the fetal heart. Peak velocities of the E wave and the A wave, were recorded. The E/A ratio, which is an index for ventricular diastolic function and expresses both cardiac compliance and preload conditions, was calculated [18]. Cardiac outflow flow-velocity waveforms from the aorta were recorded from the 5-chamber view and the short-axis view of the fetal heart just above the semi-lunar valves, respectively. Peak systolic velocity (PSV) and the inner diameter during systole were recorded. Left cardiac output was calculated in milliliters per minute by multiplying the vessel area by the time-velocity integral by fetal heart rate. All ultrasound examinations were performed with an ATL-Philips model HDI 5000 (Seattle, Washington, USA) equipped with a 5.0-MHz high-frequency, curved-array transducer.

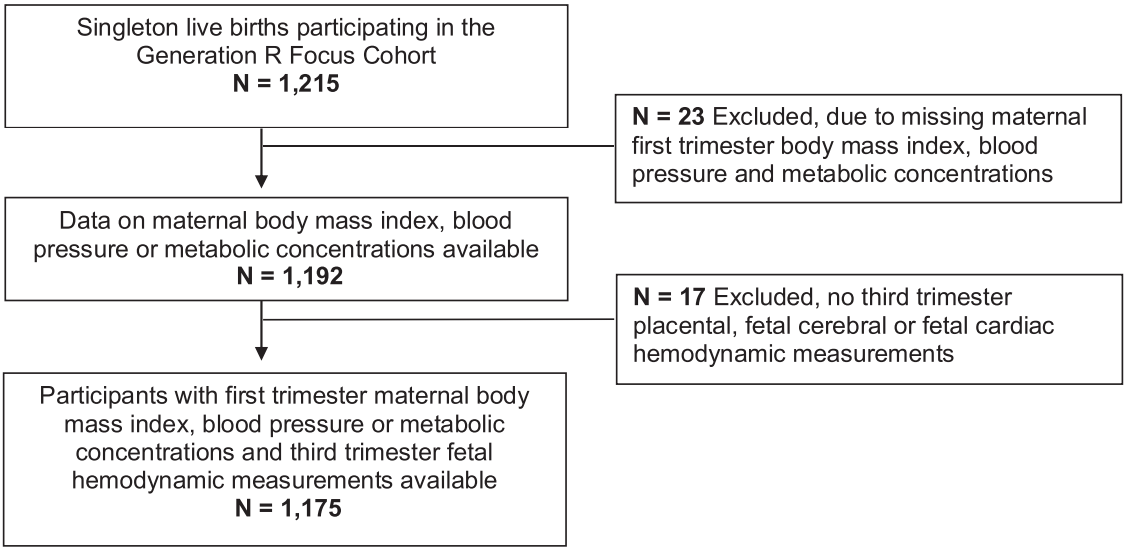

Fig. 1. Flow chart of participants included in the analysis.

Covariates

We obtained information on maternal educational level, parity, and smoking during pregnancy from multiple questionnaires during pregnancy by the mother. Third trimester estimated fetal weight was obtained during ultrasound [24]. Infant sex was obtained from midwife and hospital registries.

Statistical analyses

First, we assessed the associations of an adverse maternal early-pregnancy metabolic profile with placental, fetal cerebral and cardiac hemodynamics using multiple linear regression models. The models were adjusted for maternal age, educational level, parity, smoking status during pregnancy, third trimester gestational age, estimated fetal weight and child sex. We also performed a sensitive analysis using birth weight instead estimated fetal weight. Next, we examined the associations of each of the individual components of an adverse maternal early-pregnancy metabolic profile with placental, fetal cerebral and cardiac hemodynamics using similar models. For interpretation purposes, we also presented these associations in a graph which shows standardized predicted values for these associations obtained from the regression models. For the associations of maternal early-pregnancy blood pressure, cholesterol, triglycerides and glucose concentrations with placental and fetal hemodynamic measures, we further explored whether the associations were explained by maternal pre-pregnancy BMI. We also tested potential interaction between maternal metabolic factors and BMI for all of our analyses.

Table 1
Characteristics of mothers and their children after multiple imputation.

Maternal characteristics	Total group (N = 1.175)	Mothers with an adverse metabolic profile (N = 108, 9.2%)	Mothers without an adverse metabolic profile (N = 728, 62%)	P-value
Maternal age	31.9 (22.0–39.1)	32.4 (23.6–39.5)	31.8 (21.4–39.0)	0.7
Education (%)				<0.001
Low (no, primary, secondary education)	36.9 (434)	50.9 (55)	33.2 (242)	
High (higher education)	63.1 (741)	49.1 (53)	66.8 (486)	
Pre-pregnancy body mass index (kg/m^2)	23.5 (4.0)	28.5 (5.0)	22.7 (3.2)	<0.001
BMI > 25.0	22.4 (263)	80.6 (87)	17.7 (129)	<0.001
Parity (%)				0.8
Nullipara	60.8 (714)	61.1 (66)	62.6 (456)	
Multipara	39.2 (461)	38.9 (42)	37.4 (272)	
Smoking during pregnancy (%)				0.3
No smoking throughout pregnancy	76.1 (894)	73.1 (79)	77.7 (567)	
Yes	23.9 (281)	26.9 (29)	22.3 (161)	
Gestational hypertension (%)	6.0 (71)	12 (11.1)	37 (5.1)	0.03
Pre-eclampsia (%)	2.3 (27)	5.6 (6)	3.0 (22)	0.04
First trimester maternal characteristics				
Gestational age at measurement, weeks	12.6 (9.6–17.1)	12.9 (9.5–17.0)	12.8 (9.7–17.1)	0.7
Systolic blood pressure (mmHg)	119 (13)	134 (12)	116 (11)	<0.001
Diastolic blood pressure (mmHg)	70 (10)	80 (10)	68 (9)	<0.001
Total cholesterol, mmol/L	4.9 (0.9)	5.4 (0.9)	4.8 (0.8)	<0.001
HDL-cholesterol, mmol/L	1.8 (0.3)	1.6 (0.3)	1.8 (0.3)	<0.001
Triglycerides, mmol/L	1.3 (0.5)	1.8 (0.6)	1.2 (0.4)	<0.001
Glucose mmol/L	4.4 (0.8)	4.9 (1.0)	4.3 (0.8)	<0.001
Third trimester fetal characteristics				
Sex				0.1
Male	52.4 (616)	59.3 (64)	51.0 (371)	
Female	47.6 (559)	40.7 (44)	49.0 (357)	
Gestational age at measurement, weeks	30.3 (27.4–32.6)	30.2 (28.6–32.3)	30.4 (28.4–32.7)	<0.01
Estimated fetal weight, grams	1628 (268)	1609 (265)	1624 (275)	0.6
Third trimester feto-placental hemodynamics				
Uterine artery RI	0.49 (0.08)	0.49 (0.08)	0.49 (0.07)	0.9
Umbilical artery PI	0.97 (0.17)	0.97 (0.16)	0.97 (0.17)	0.6
Third trimester fetal cerebral hemodynamics				
Middle cerebral artery PI	1.97 (0.33)	2.07 (0.30)	1.96 (0.34)	<0.01
Umbilical/Middle cerebral artery ratio	0.50 (0.11)	0.48 (0.09)	0.51 (0.12)	<0.01
Third trimester fetal cardiac hemodynamics				
Aorta ascendens diameter (cm)	0.64 (0.07)	0.64 (0.07)	0.65 (0.07)	0.4
Aorta ascendens PSV (cm/s)	91.3 (12.4)	92.1 (13.6)	91.1 (12.6)	0.5
Left cardiac output (ml/min)	606 (173)	593 (165)	615 (183)	0.3
Mitral valve E/A ratio	0.78 (0.10)	0.78 (0.09)	0.78 (0.10)	0.9
Birth characteristics				
Mode of Delivery (%)				<0.01
Vaginal, spontaneous	69.6 (818)	57.4 (62)	70.3 (512)	
Vaginal, delivery induced	10.5 (123)	20.4 (22)	10.2 (74)	
Cesarean section	13.1 (154)	18.5 (20)	12.1 (88)	
Unknown	9.5 (80)	3.7 (4)	7.4 (54)	
Apgar score (5 min), %	9.6 (0.8)	9.5 (0.8)	9.6 (0.8)	0.1
Gestational age at birth, weeks	40.3 (35.9–42.4)	40.0 (34.7–42.4)	40.3 (35.9–42.4)	0.6
Preterm birth (<37 weeks), %	4.2 (49)	4.6 (5)	4.0 (29)	0.8
Birth weight, g	3517 (541)	3539 (584)	3499 (529)	0.5
Low birth weight (<2500 g), %	3.9 (46)	4 (3.7)	3.7 (27)	0.9

Values are means (standard deviation), medians (95 % range) or valid percentages (absolute numbers). RI: resistance index, PI: pulsatility index, PSV: Peak Systolic Volume. Mothers with and without an adverse metabolic profile were compared using independent samples *t*-test for continuous variables and chi-square test for categorical variables.

No significant interactions were present and no further stratified analyses were performed. Finally, we examined the associations of change in maternal weight and blood pressure from early-pregnancy until 30 weeks of pregnancy with third trimester placental, fetal cerebral and cardiac hemodynamics using the same multiple linear regression models. The percentages of missing covariate values within the population for analyses was lower than 13 %. Missing covariate data were imputed using the multiple imputations procedure (n = 5 imputations) and the imputed datasets were analyzed together. No major differences in the effect estimates were observed between analyses with imputed missing data and complete cases only (data not shown). All measures of associations are presented within their 95 % confidence intervals (CI). Statistical analyses were performed using SPSS version 24.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Participants characteristics

Table 1 shows the population characteristics. 22.5 % of the mothers were overweight or obese at the start of pregnancy and 9.2 % of the mothers had an adverse metabolic profile at the start of their pregnancy. During pregnancy 6.0 % and 2.3 % of the mothers developed gestational hypertension and pre-eclampsia, respectively. The median gestational age was 40.3 (35.9–42.4) and the

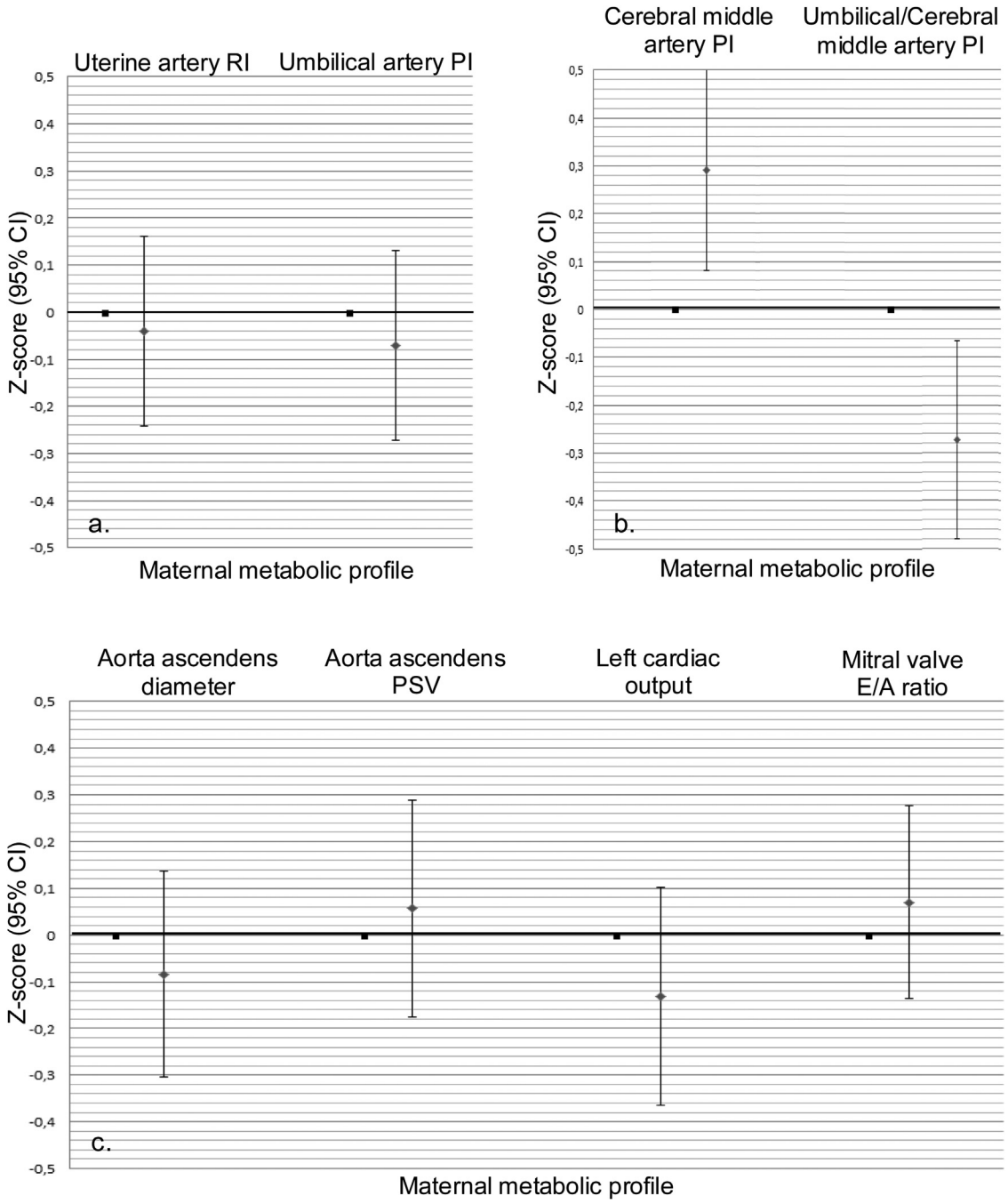

Fig. 2. Associations of maternal adverse metabolic profile with third trimester placental (a), fetal cerebral (b) and fetal cardiac hemodynamics (c).

mean birth weight of the children was 3517 (SD 541). **Table S1** shows the participant characteristics before multiple imputation.

Third trimester placental hemodynamics

Fig. 2a shows no associations were present of an adverse maternal metabolic profile with uterine artery RI and umbilical artery PI. Similarly, none of the individual components of an adverse maternal metabolic profile were associated with placental hemodynamics (Table 2**, Figure S1**).

Third trimester fetal cerebral hemodynamics

Mothers with an adverse metabolic profile had a 0.29 (95 % CI 0.08, 0.50) Z-score increase in the fetal cerebral middle artery PI compared to mothers without an adverse metabolic profile (Fig. 2b). When we assessed the individual components of an adverse maternal metabolic profile separately, higher total maternal cholesterol and triglyceride concentrations were associated with a higher cerebral middle artery PI (Table 3**, Figure S2** Z-score, 0.09 (95 % CI 0.02, 0.15), 0.09 (95 % CI 0.03, 0.15) per Z-score increase in total cholesterol and triglyceride concentrations, respectively). These associations were not explained by maternal BMI. No associations of maternal pre-pregnancy BMI, blood pressure, HDL-cholesterol and glucose concentrations with fetal cerebral hemodynamics were present. The associations with the fetal U/C ratio were similar (Fig. 2, Table 2).

Third trimester fetal cardiac hemodynamics

An adverse maternal metabolic profile was not associated with fetal cardiac hemodynamics (Fig. 2c). When we assessed the associations of individual components of an adverse maternal metabolic profile with fetal cardiac hemodynamics, a higher maternal diastolic blood pressure, total and HDL-cholesterol concentrations were associated with a higher fetal left cardiac output (Table 4, Z-score 0.08 (95 % CI 0.02, 0.15), 0.07 (95 % CI 0.01, 0.13), 0.11 (95 % CI 0.05, 0.18) per Z-score increase in diastolic blood pressure, total and HDL-cholesterol concentrations, respectively). Higher maternal HDL-cholesterol concentrations were associated with a larger aorta ascendens diameter and aorta ascendens PSV (Z-score 0.10 (95 % CI 0.04, 0.17), 0.08 (95 % CI 0.01, 0.14) per Z-score increase in HDL-cholesterol concentrations). Total maternal cholesterol concentrations were also associated with a higher aorta ascendens PSV (Z-score 0.08 (95 % CI 0.01, 0.14) per Z-score increase in total cholesterol concentrations). These associations were not explained by adjustment for maternal pre-pregnancy BMI. No associations of maternal triglyceride or glucose concentrations with fetal cardiac hemodynamics were present. Similar findings were present when we used birth weight instead of estimated fetal weight (results not shown). For visual interpretation we showed in **Figure S3** the standardized regression prediction values of the multiple linear regression models of maternal pre-pregnancy BMI, total cholesterol, triglyceride and glucose concentrations with third trimester fetal cardiac hemodynamics in graph format. Table 5 shows that maternal weight gain was associated with a larger aorta ascendens diameter and an increase in cardiac output (Z-score 0.02 (95 % CI 0.01, 0.04) and 0.02 (95 % CI 0.01, 0.04) per increase in weight gain, respectively). Higher increase in maternal systolic blood pressure was associated with a higher uterine artery RI and umbilical artery PI (Z-score 0.09, (95 % CI 0.03, 0.15) and 0.08 (95 % CI 0.02, 0.15) per increase in blood pressure, respectively) and a decrease in aorta ascendens diameter and left cardiac output (Z-score -0.07 (95 % CI -0.13, -0.01) and -0.07 (95 % CI -0.13, -0.01) per increase in blood pressure), whereas a higher increase in diastolic blood pressure was associated with a higher umbilical artery PI (Z-score 0.06 (95 % CI 0.00, 0.12)).

Table 2
Associations of early pregnancy maternal BMI, blood pressure and first trimester metabolic concentrations with third trimester utero-placental and feto-placental hemodynamics (n = 1175).

	Uterine artery RI Z-score (95 % CI)	Umbilical artery PI Z-score (95 % CI)
Pre-pregnancy BMI (Z-score)	0.06 (-0.00, 0.12)	0.06 (-0.01, 0.12)
Systolic blood pressure (Z-score)	0.07 (-0.01, 0.16)	0.00 (-0.06, 0.06)
Diastolic blood pressure (Z-score)	0.01 (-0.05, 0.08)	−0.01 (-0.07, 0.06)
Total cholesterol (Z-score)	−0.03 (-0.09, 0.03)	0.00 (-0.06, 0.06)
HDL-cholesterol (Z-score)	−0.00 (-0.07, 0.06)	−0.05 (-0.11, 0.01)
Triglycerides (Z-score)	−0.01 (-0.07, 0.05)	0.05 (-0.02, 0.11)
Glucose (Z-score)	0.06 (-0.01, 0.12)	−0.01 (-0.07, 0.06)

Values are regression coefficients (95 % confidence intervals) and reflect the change in Z-score of placental indexes per Z-score change in maternal BMI, blood pressure and metabolic concentrations. The models are adjusted for maternal age, educational level, parity, smoking status during pregnancy, third trimester gestational age and estimated fetal weight, and child sex. RI: resistance index, PI: pulsatility index.

Discussion

Main findings

In this population prospective cohort study we observed that an adverse maternal early-pregnancy metabolic profile, especially higher maternal cholesterol and triglycerides concentrations, were associated with increased fetal cerebral vascular resistance and larger fetal aorta ascendens diameter, PSV and left cardiac output, but not with placental vascular resistance indices. These associations were not explained by maternal BMI.

Interpretation

Maternal pre-pregnancy obesity is strongly related to metabolic disturbances during pregnancy [1,2]. Both maternal pre-pregnancy obesity and these subsequent metabolic disturbances are major risk factors for pregnancy complications and adverse birth outcomes [3]. The underlying mechanisms are not known, but might be related to impaired placental growth and function [4]. The placenta can be considered as the interface between the maternal and fetal environment and the major regulator of fetal nutrition, growth and cardiovascular development [25]. Multiple studies have shown that maternal obesity is related to larger placental weight [26]. Several studies also showed that individual components of an adverse maternal metabolic profile, such as high blood pressure, high triglycerides, adverse cholesterol profile and high glucose concentrations are associated with both low and high placental weight at birth [27–29], which suggest various mechanisms may be involved. An adverse maternal metabolic profile may lead to a pro-inflammatory state leading to reduced placental vascularization, placental infarction and reduced placenta growth, whereas an adverse maternal metabolic profile may also lead to increased nutrient transfer to the placental, larger placental growth and accelerate fetal growth [8].

Placental weight is only a crude measurement of placental development and function during pregnancy. More detailed measures of placental function can be assessed by Doppler ultrasound of the umbilical and uterine arteries during pregnancy. A higher uterine RI and umbilical artery PI indicated a higher peripheral vascular resistance [19,20]. We observed no associations of maternal metabolic profile with the uterine and umbilical artery vascular resistance. A few other studies explored the associations of individual components of an adverse maternal metabolic profile with uterine and umbilical artery vascular

Table 3
Associations of early pregnancy maternal BMI, blood pressure, and first trimester metabolic concentrations with third trimester fetal cerebral hemodynamics (n = 1175).

	Cerebral middle artery PI Z-score (95% CI)	Umbilical/Cerebral middle artery PI ratio Z-score (95 % CI)
Pre-pregnancy BMI (Z-score)	0.05 (-0.01, 0.12)	−0.01 (-0.07, 0.06)
Systolic blood pressure (Z-score)	0.05 (-0.01, 0.12)	−0.03 (-0.09, 0.03)
Diastolic blood pressure (Z-score)	0.05 (-0.02, 0.11)	−0.03 (-0.09, 0.04)
Total cholesterol (Z-score)	0.09 (0.02, 0.15)†	−0.07 (-0.13, -0.01)*
+pre-pregnancy BMI	0.08 (0.02, 0.15)*	−0.07 (-0.13, -0.01)*
HDL-cholesterol (Z-score)	−0.04 (-0.10, 0.03)	−0.02 (-0.09, 0.04)
Triglycerides (Z-score)	0.09 (0.03, 0.15)†	−0.03 (-0.10, 0.03)
+pre-pregnancy BMI	0.09 (0.02, 0.15)†	
Glucose (Z-score)	0.02 (-0.04, 0.09)	−0.02 (-0.09, 0.04)

Values are regression coefficients (95 % confidence intervals) and reflect the change in Z-score of fetal cerebral indexes per Z-score change in maternal BMI, blood pressure and metabolic concentrations. The models are adjusted for maternal age, educational level, parity, smoking status during pregnancy, third trimester gestational age and estimated fetal weight, and child sex. PI: pulsatility index. *=P<0.05, †=P<0.01.

Table 4
Associations of early pregnancy maternal BMI, blood pressure and first trimester metabolic concentrations with third trimester fetal cardiac hemodynamics (n = 1175).

	Aorta ascendens diameter Z-score (95 % CI)	Aorta ascendens PSV Z-score (95 % CI)	Left cardiac output Z-score (95 % CI)	Mitral valve E/A ratio Z-score (95 % CI)
Pre-pregnancy BMI (Z-score)	−0.02 (-0.09, 0.04)	0.00 (-0.07, 0.07)	−0.03 (-0.10, 0.04)	0.01 (-0.05, 0.08)
Systolic blood pressure (Z-score)	0.01 (-0.06, 0.07)	0.00 (-0.07, 0.07)	0.01 (-0.06, 0.07)	0.03 (-0.03, 0.09)
Diastolic blood pressure (Z-score)	0.04 (-0.02, 0.10)	0.03 (-0.04, 0.09)	0.08 (0.02, 0.15)†	0.01 (-0.05, 0.07)
+pre-pregnancy BMI			0.12 (0.05, 0.20)†	
Total cholesterol (Z-score)	0.02 (-0.04, 0.08)	0.08 (0.01, 0.14)*	0.07 (0.01, 0.13)*	−0.01 (-0.08, 0.05)
+pre-pregnancy BMI		0.08 (0.01, 0.15)*	0.07 (0.01, 0.14)*	
HDL-cholesterol (Z-score)	0.10 (0.04, 0.17)†	0.08 (0.01, 0.14)*	0.11 (0.05, 0.18)†	−0.05 (-0.11, 0.02)
+pre-pregnancy BMI	0.10 (0.04, 0.16)†	0.07 (0.00, 0.14)*	0.11 (0.04, 0.17)†	
Triglycerides (Z-score)	−0.03 (-0.10, 0.03)	0.04 (-0.03, 0.10)	0.01 (-0.06, 0.07)	0.00 (-0.06, 0.07)
Glucose (Z-score)	−0.01 (-0.07, 0.05)	0.05 (-0.02, 0.11)	−0.02 (-0.08, 0.05)	−0.05 (-0.12, 0.02)

Values are regression coefficients (95 % confidence intervals) and reflect the change in Z-score of fetal cardiac hemodynamics per Z-score change in maternal BMI, blood pressure and metabolic concentrations. The models are adjusted for maternal age, educational level, parity, smoking status during pregnancy, third trimester gestational age and estimated fetal weight, and child sex. PSV: Peak Systolic Volume. *=P<0.05, †=P<0.01.

Table 5
Associations of maternal weight gain during pregnancy, and third trimester blood pressure with third trimester fetal placental, cerebral and cardiac hemodynamics (n = 1175).

	Maternal weight gain during pregnancy	Maternal third trimester systolic blood pressure (Z-score)	Maternal third trimester diastolic blood pressure (Z-score)
Uterine artery RI, Z-score (95 % **CI**)	0.00 (-0.01, 0.01)	0.09 (0.03, 0.15)†	0.05 (-0.01, 0.11)
Umbilical artery PI, Z-score (95 % **CI**)	0.00 (-0.02, 0.01)	0.08 (0.02, 0.15)†	0.06 (0.00, 0.12)*
Cerebral middle artery PI, Z-score (95 % **CI**)	−0.01 (-0.02, 0.01)	0.03 (-0.03, 0.09)	0.04 (-0.02, 0.10)
Aorta ascendens diameter, Z-score (95 % **CI**)	0.02 (0.01, 0.04)*	−0.07 (-0.13, -0.01)*	0.01 (-0.05, 0.07)
Aorta ascendens PSV, Z-score (95 % **CI**)	−0.01 (-0.02, 0.01)	−0.02 (-0.09, 0.04)	−0.04 (-0.11, 0.02)
Left cardiac output, Z-score (95 % **CI**)	0.02 (0.01, 0.04)†	−0.07 (-0.13, -0.01)*	0.00 (-0.06, 0.06)
Mitral valve E/A ratio, Z-score (95 % **CI**)	0.00 (-0.01, 0.02)	−0.02 (-0.08, 0.04)	0.01 (-0.05, 0.07)

Values are regression coefficients (95 % confidence intervals) and reflect the change in Z-score of fetal hemodynamics per change in maternal weight gain and z-score change in blood pressure. The models are adjusted for maternal age, educational level, parity, smoking status during pregnancy, third trimester gestational age and estimated fetal weight, and child sex. PSV: Peak Systolic Volume. *=P<0.05, †=P<0.01.

resistance in pregnancy. A previous prospective study focused on 231 women affected by hypertensive disorders showed a higher uterine artery PI compared with normative pregnancies [30]. Among 10 women with familial hypercholesterolemia, it was observed that the PI of the uterine arteries was similar at 24 weeks of gestation, and remained unaltered at 36 weeks of gestation, in contrast to a decrease in the reference group [31]. An intervention study among 290 pregnant women demonstrate a more pronounced gestational decrease in the umbilical artery PI between 24 and 30 weeks of pregnancy after following a low-cholesterol low-saturated fat diet [32]. Two studies among Chilean women showed a correlation of total- and LDL-cholesterol concentrations, but not triglyceride concentrations, with lower sensitivity of the umbilical vein rings and reactivity, a phenomena that is likely due to endothelial dysfunction [33,34]. Differences between our study and previous studies may be explained by differences in study population. We studied women with relatively healthy pregnancies and assessed associations across the full range of maternal metabolic factors, whereas many of the previous studies focused on high-risk populations and women with clinically abnormal metabolic parameters, such as clinical hypercholesterolemia. This may suggest that associations with uterine and umbilical vascular resistance are only present at the extremes of these adverse maternal metabolic factors, but not across the full range.

Consequences of impaired placentation might lead to redistribution of blood flow, with increased fetal blood to the brain and heart of the fetus due to reduced oxygen supply and its influence on fetal vascular development. The middle cerebral artery PI quantifies the redistribution of blood flow, and when lower, in favor of the fetal brain. An indicator of the 'brain-sparing effect' is a raised ratio between the umbilical artery PI and the cerebral artery PI (U/C ratio) [23]. In line with previous studies from the same cohort we used the

U/C ratio, and not the Cerebrum Placental ratio (CPR) which reflects cerebral artery PI/umbilical artery PI ratio. These measurements have an inverse 1:1 correlation [35–37]. To the best of our knowledge, not many data on fetal hemodynamic reference data are available and they describe different populations which makes comparisons difficult [38]. However, our study is focused on the associations of maternal metabolic factors with fetal hemodynamic parameters in which we show differences in these fetal hemodynamic parameters by maternal metabolic factors. Further studies are needed to replicate our findings in different populations and to examine the effects on absolute values of the fetal hemodynamic parameters.We observed that an adverse maternal early-pregnancy metabolic profile was associated with increased fetal cerebral vascular resistance. These associations were mainly present for high cholesterol and triglyceride concentrations. Higher cholesterol concentrations were also associated with a larger fetal left cardiac output, larger aorta ascendens diameter and larger aorta ascendens PSV. Our findings thus suggest that increased maternal cholesterol and triglycerides levels, still within the normal range (reference range total cholesterol concentrations, women 50th centile 5.0 (95 % range 3.3–7.3), triglyceride concentrations, 50th centile 1.0 (95 % range 0.4–2.9) (39)), lead to increased fetal cerebral resistance indexes and aorta ascendens diameter, aorta ascendens PSV and cardiac output suggesting a 'reverse' redistribution in favor of increased cardiac growth. The findings were not explained by maternal BMI, suggesting effects of maternal cholesterol and triglyceride concentrations within the normal range were independent of BMI. In line with our findings, results from the same study cohort also showed that maternal triglyceride and cholesterol levels are associated with increased fetal growth rates which resulted in a higher birth weight [40]. These findings might suggest that these increased maternal lipid levels have consequences for fetal cardiac development and might lead to persistent subclinical consequences in childhood. Longitudinal studies reported tracking of risk factors for cardiovascular disease during childhood [41,42]. Also the consequences of fetal adaptations might not be detectable during fetal life, but might become more evident in early adulthood. It had been suggested that fetal adaptations can be compensated for many years until for example hypertension occurs [43]. No other previous studies explored the associations of maternal cholesterol or triglycerides concentrations with fetal cerebral vascular resistance or fetal cardiac hemodynamics. However, the effect estimates are small and are mainly relevant on a population level providing further insight into pathophysiological mechanisms. Further studies are needed to replicate our findings, to explore these associations throughout pregnancy and to assess the consequences for both birth outcomes and long-term offspring outcomes.

Strengths and limitations

The main strength of this study is the large population-based cohort studied. To our knowledge, this is the largest study, which examined the effects of maternal metabolic factors on placental and fetal hemodynamics. The population-based setting enabled us to assess maternal metabolic factors and placental and fetal hemodynamic measures across the full range, rather than only in mothers or fetuses with complications. However, because of our relatively healthy population, it should be further studied whether the observed associations are generalizable to high-risk populations. We observed that increased weight gain was associated with an increased third trimester fetal cardiac aorta ascendens diameter and left cardiac output. An increase in maternal third trimester systolic blood pressure was associated with an increased uterine and umbilical artery resistance index, but a smaller fetal third trimester aorta ascendens diameter and left cardiac output. Interestingly, we did not found associations of first trimester maternal BMI and blood pressure with third trimester fetal hemodynamics. We only measured maternal glucose, cholesterol and triglyceride concentrations once during pregnancy. However, it has been suggested that impaired glucose control in early pregnancy persists throughout pregnancy [44]. Similarly, cholesterol and triglyceride concentrations are elevated during all three trimesters of pregnancy in women with gestational diabetes [45]. Further studies are needed with repeat maternal glucose and lipids concentrations measurements throughout pregnancy to replicate our findings and to identify the critical periods for feto-placental hemodynamic adaptations. In the present study, we evaluated multiple associations; this might have led to chance findings due to multiple testing. However, because of the correlations between the fetal hemodynamic measures we did not correct for multiple testing. Missing fetal hemodynamic measurements could lead to selection bias and loss of power. Our results would be biased if the associations between maternal metabolic factors and fetal hemodynamics differ between those included and those not included in the study. Although this seems unlikely, it cannot be excluded. Finally, although we had information about a large number of confounders, the influence of residual confounding should be considered, as in any observational study.

Conclusions

An adverse maternal metabolic profile, especially higher maternal cholesterol and triglycerides concentrations still within the normal range, were associated with increased fetal cerebral vascular resistance and increased fetal cardiac hemodynamics, but not with placental vascular resistance indices.

Contribution to authorship

MNK and RG were responsible for the statistical analyses, the interpretation of the data and the revisions of the manuscript. MNK also wrote the first draft of the manuscript. RG was responsible for the original research idea, and supervised MNK with data analysis, interpretation of the data, and writing and revision of the manuscript. EAPS contributed to the interpretation of the data, and critically revised the manuscript. VWVJ initiated and designed the study, was responsible for the infrastructure in which the study was conducted, contributed to the original data collection, and critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

Details of ethics approval

Written informed consent was obtained from all participants. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam (December 2001, MEC 198.782.2001.31).

Data availability statement

Data requests can be made to the secretariat of Generation R.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2020.12.011.

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