Published in final edited form as:

BJOG. 2016 December ; 123(13): 2104–2112. doi:10.1111/1471-0528.13933.

Influence of fetal blood flow redistribution on fetal and childhood growth and fat distribution. The Generation R Study

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Abstract

Objective—A suboptimal intra-uterine environment leads to fetal blood flow redistribution and fetal growth restriction. Not much is known about childhood growth consequences. We examined the associations of fetal blood flow redistribution with birth outcomes, repeatedly measured fetal and childhood growth and fat mass measures.

Design—Prospective cohort study.

Setting—Population-based.

Population—1,195 pregnant women and their children.

Methods—We measured umbilical and cerebral artery blood flow at a gestational age of 30.3 weeks (95% range 28.5–32.6). A higher umbilical/cerebral (U/C) pulsatility index ratio is an

This is the peer reviewed version of the following article: Kooijman MN, Gaillard R, Reiss IKM, Hofman A, Steegers EAP, Jaddoe VWV. Influence of fetal blood flow redistribution on fetal and childhood growth and fat distribution: the Generation R Study. BJOG 2016;123:2104–2112, which has been published in final form at <http://onlinelibrary.wiley.com/doi/10.1111/1471-0528.13933/full>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

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Disclosure of interests

None.

Contribution to Authorship

Marjolein Kooijman and Romy Gaillard were responsible for the statistical analyses, the interpretation of the data, and the revisions of the manuscript. Marjolein Kooijman also wrote the first draft of the manuscript. Vincent Jaddoe is responsible for the original research idea, and supervised Marjolein Kooijman with data-analysis, interpretation of the data, and writing and revising of the manuscript. Irwin Reiss and Eric Steegers contributed to the interpretation of the data, and critically revised the manuscript. Albert Hofman and Vincent Jaddoe initiated and designed the study, were 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 of the final version of the manuscript.

Details of Ethics Approval

Written informed consent was obtained from all participants. The study has been approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam.

indicator of preferential blood flow to the brain cerebral circulation at expense of the lower body parts.

Main Outcome Measures—Fetal and childhood growth were repeatedly measured from third trimester until childhood. We measured total body fat mass, lean fat mass and android/gynoid fat mass ratio by dual-energy x-ray absorptiometry and preperitoneal fat by ultrasound at 6 years.

Results—A higher fetal U/C ratio was associated with increased risks of preterm birth and small size for gestational age at birth (Odds Ratios 1.41 (95% CI 1.08 to 1.85) and 1.63 (1.21 to 2.19), respectively per SD increase in U/C ratio). Longitudinal growth analyses showed that a higher fetal U/C ratio was associated with persistently lower head circumference, length, and weight from third trimester fetal life until childhood (all p-values <0.05). Fetal U/C ratio was not associated with total body and abdominal fat measures at 6 years.

Conclusion—Our results suggest that fetal blood flow redistribution affects fetal development and has persistent consequences for childhood growth.

Keywords

Fetal and placental circulation; Fetal haemodynamics; Doppler ultrasound; Epidemiology; Childhood growth; Adiposity

Introduction

Fetal growth and development largely depends on an adequate placental and fetal circulation.(1) An adverse intra-uterine environment leads to fetal blood flow redistribution with a preferential fetal blood flow to the brain cerebral circulation at the expense of lower body parts.(2, 3) This fetal blood flow distribution leads to relatively higher blood and oxygen supply to the brains and heart.(4, 5) Fetal blood flow redistribution is caused by higher peripheral and lower cerebral vascular resistance, and can be measured as a higher umbilical artery pulsatility index (PI) and a lower cerebral PI.(2) This combination leads to a higher umbilical/cerebral (U/C) ratio.(6) Previous studies have shown that fetal blood flow redistribution in late pregnancy might be accompanied with asymmetrical fetal growth restriction characterized by a relatively larger head size than body size at birth.(7–9) Subsequently, this can lead to a different body composition and increased percentages of body fat in later life.(10) Previously, we observed that third trimester uterine, umbilical and cerebral blood flow measures are correlated with a lower estimated fetal weight.(11) We also observed that an increased third trimester umbilical artery vascular resistance is associated with lower fetal length and weight growth in third trimester resulting in smaller size at birth.(12) These differences in length and weight growth characteristics became smaller from the age of 6 months, but were still present at the age of 6 years.(12) Thus far, it is not known whether only umbilical artery flow changes or also cerebral artery flow changes affect childhood growth and body fat distribution.

We examined in a population-based prospective cohort study among 1,195 pregnant women and their children, the associations of third trimester fetal blood flow redistribution with repeatedly measured fetal and childhood growth characteristics and fat distribution outcomes.

Methods

Design and study population

The current study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life onwards in Rotterdam, the Netherlands.(13, 14) The Medical Ethics Committee of the Erasmus MC, University Medical Center, Rotterdam, has approved the study. The study has been described in detail previously. Briefly, all participating were born between April 2002 and January 2006. Enrollment was aimed at early pregnancy but allowed until birth of the child. In total, 9,778 mothers and their children were enrolled in the study. More detailed assessments of fetal and childhood growth and development were conducted in a random subgroup of 1,232 Dutch mothers and children.(13) For the present analysis, twin pregnancies (n=15) and pregnancies leading to perinatal death (n=2) were excluded from this analyses, resulting in 1,215 singleton live born children. Third trimester fetal blood flow distribution measurements were available in 1,195 children (Supplementary Material Figure S1). Of all of these children, at least one growth measure was available.

Third trimester fetal blood flow distribution

In the Netherlands, routinely ultrasound scans are performed at 12 and 20 weeks of gestation. For this study, third trimester fetal ultrasound examinations were performed at a median gestational age of 30.3 (95% range 28.5 – 32.6) weeks. Gestational age was established by first trimester ultrasound measurements.(15) Fetal blood flow distribution was measured as inverse of the corresponding resistance indices in the umbilical and cerebral artery by pulsed-wave Doppler, as described previously.(16–18) A higher pulsatility index (PI) in a fetal artery might be an indication of a lower blood flow and an increased vascular resistance.(19) For all Doppler measurements, colour imaging was used to optimize placement of the pulsed-wave Doppler gate. The mean of three measurements was used for analyses. The redistribution of blood flow in favour of the fetal brain was quantified by the middle cerebral artery PI.(20) Middle cerebral artery Doppler measurements were performed with colour Doppler visualization of the circle of Willis in the fetal brain, and flow-velocity waveforms were obtained in the proximal part of the cerebral arteries. Fetal blood flow redistribution in favour to the brain at expense of the trunk, including the abdominal organs, is indicated by an increased ratio between the umbilical artery PI and the cerebral artery PI (higher U/C ratio).(6) Intra- and interobserver analyses showed good reproducibility for all Doppler measurements, as described previously (all intra-class correlation coefficients > 0.80).(11) The mean and SD of the umbilical and cerebral artery PI observed in our study were in line with a previous longitudinal study focused on serial measurements.(21) Variables were normally distributed, as shown in Supplementary Material Figure S6.

Fetal and childhood growth

During the same visit in third trimester, we measured fetal head circumference, abdominal circumference, femur length and calculated estimated fetal weight.(15, 22) Gestational age adjusted standard deviation scores were constructed for all fetal growth measurements(23). We obtained information on date of birth, birth anthropometrics (head circumference, length, weight) and offspring sex from community midwife and hospital registries. Preterm birth was defined as a gestational age of <37 weeks at birth. Small size for gestational age at birth

was defined as gestational age corrected birth weight below the fifth centile in the study cohort. Since head circumference and length at birth were not routinely measured at birth, missing birth measures were completed with data from the first month visit at the child health center. Well-trained staff obtained postnatal growth characteristics (head circumference, height, weight) using standardized procedures. Visits were scheduled for age 6 months (median: 6.2, 95% range: 5.2 – 7.8), 12 months (median: 11.0, 95% range: 10.1 – 12.6), 24 months (median: 24.9, 95% range: 23.4 – 28.2), 36 months (median: 37.8, 95% range: 35.4 – 40.7), 48 months (median: 45.8, 95% range: 44.5 – 48.4) and 72 (95% range: 68.4 – 79.2) months. Head circumference was measured by a measuring tape (SECA). We measured length in infants in supine position to the nearest 0.1cm by a neonanometer (Holtain Limited) and after this period by a Harpenden stadiometer (Holtain Limited) in standing position. Weight was measured in naked infants at the age of 6 months to the nearest grams by using an electronic infant scale (SECA) and from 24 months onwards by a mechanical personal scale (SECA). We calculated body mass index (kg/m^2). For postnatal growth characteristics, we calculated standard deviation scores using Dutch reference growth curves(24) (Growth Analyzer 3.0, Dutch Growth Research Foundation, Rotterdam, the Netherlands).

Childhood adiposity outcomes

We measured total body and regional fat mass using a Dual energy X-ray absorptiometry (DXA) scanner (iDXA, GE-Lunar, 2008, Madison, WI, USA) and analysed with the enCORE software v.12.6(25). DXA can accurately detect whole-body fat mass within less than 0.25% coefficient of variation. Children were placed without shoes, heavy clothing and metal objects in supine position on the DXA table. Total fat mass (kg) and lean mass were calculated as percentage of total body weight (kg) measured by DXA. The android/gynoid fat mass ratio was calculated. The android/gynoid fat ratio reflects the central body fat distribution in the abdomen and hip regions, respectively and was used as a marker of waist/hip fat distribution.(26)

Abdominal ultrasound examinations were performed with ultrasound, as described in detail. (27, 28) Briefly, preperitoneal fat thicknesses were measured with a linear transducer(27) , which was placed perpendicular to the skin surface on the median upper abdomen. We scanned longitudinally just below the xiphoid process to the navel along the midline (linea alba). All measurements were performed off-line. Preperitoneal fat mass distance was measured as distance of the linea alba to the peritoneum on top of the liver. Preperitoneal fat mass area was measured as area of 2 cm length along the midline starting from the maximum preperitoneal distance in direction of the area. We measured three times the areas of 2 cm length along midline, and we used the mean value of these measures. The intra-observer reproducibility and the intra-class correlation coefficients showed good reproducibility (all intra-class correlation coefficients > 0.92). (29)

Covariates

We obtained information on maternal age, prepregnancy weight, parity, educational level, smoking during pregnancy, folic acid use, gestational hypertensive disorders (gestational hypertension/preeclampsia) and gestational diabetes by questionnaires and medical records.

We measured maternal height without shoes and we calculated prepregnancy body mass index (kg/m^2).

Statistical analysis

First, we used multivariate logistic regression models to examine the associations of third trimester fetal blood flow distribution (umbilical artery PI, middle cerebral artery PI and U/C ratio) with the risks of preterm birth and small size for gestational age at birth. The models were first adjusted for gestational age at third trimester measurement and child sex (basic model). Additionally, we included potential confounders including maternal age, parity, educational level, pre-pregnancy body mass index, smoking status during pregnancy, folic acid supplementation use, and pregnancy complications (confounder model). Second, the associations of third trimester fetal blood flow redistribution (umbilical artery PI, middle cerebral artery PI and U/C ratio) were analysed using unbalanced repeated measurement regression models. These models take the correlation between repeated measurements of the subject into account and allow for incomplete outcome data.(30, 31) We created fetal and childhood models in which gestational or childhood age were included as continuous variables. From the constructed models, we obtained effect estimates at specific time points of interest. The fetal flow measurements were included in the models as intercept, which reflects the mean SDS for each growth characteristics per SD increase in U/C ratio, and as interaction term with gestational/postnatal age. This interaction term reflects the difference in change in growth characteristics over time per SD increase in U/C ratio. We used a compound symmetry covariance structure. The models are described in more detail in the Supplementary Material. Furthermore, we performed similar analyses focused on the associations of U/C ratio with childhood growth in groups of children with the lowest third trimester estimated fetal weight (<10% of EFW) and highest third trimester estimated fetal weight (> 90% of EFW). Third, we used multivariate linear regression models to examine the associations of fetal blood flow distribution (umbilical artery PI, middle cerebral artery PI and U/C ratio) with childhood fat measures. As preperitoneal fat area had a skewed distribution, we applied natural log-transformation. The models were first adjusted for gestational age and estimated fetal weight at third trimester measurement, child sex and current age. Additionally, we included same potential confounders as for the birth outcome models. The models with childhood fat and lean mass as outcome were also adjusted for height at time of the fat measurements. Covariates were included in the models based on their association with fetal blood flow distribution and growth measurements as shown in previous studies.(12) The confounder models were considered as the main models. We tested potential interactions between fetal blood flow distribution and sex for all our analyses. Significant interactions were present for the repeated measured head circumference in pre- and postnatal models and prenatal measured length ($p < 0.05$). All these analyses were performed for total group, and for boys and girls separately. All effect estimates were given per standard deviation (SD) change in fetal blood flow distribution measures. To reduce the possibility of potential bias associated with missing data (less than 18%), missing values were imputed using the multiple imputations procedure. In the imputation model we included all covariates. Five imputed datasets were created and analyzed together. Further information about the methods of multiple imputations are given in the Supplementary Material. The repeated measurement analyses were performed using

the Statistical Analysis System version 9.3 (SAS, Institute Inc. Cary NC). All other analyses were performed using the Statistical Package for the Social Sciences version 21.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

Participant characteristics

Table 1 showed a mean umbilical artery PI of 0.97 (0.16), a middle cerebral artery PI of 1.97 (0.16), and an U/C ratio of 0.50 (0.11). At age 6 years, children had a mean body length of 119.0 (5.2) cm, weight of 22.6 (3.2) kg and the mean total fat mass was 23.8 (4.5)%.

Descriptive data of the participants without multiple imputation are shown in Supplementary Material Table S1. Supplementary Material Table S2 shows all infant growth characteristics, Table S3 shows maternal characteristics.

Third trimester fetal flow distribution and the risks of adverse birth outcomes

Table 2 shows that a higher third trimester fetal U/C ratio was associated with increased risk of preterm birth (OR 1.41 (95% CI 1.08 to 1.85) per SD increase in fetal U/C ratio) and small for gestational age (OR 1.63 (95% CI 1.21, 2.19) per SD increase in fetal U/C ratio).

Third trimester fetal flow distribution and longitudinal growth measurements

Figure 1 shows the associations of third trimester fetal U/C ratio with longitudinal fetal and childhood growth patterns. A higher third trimester fetal U/C ratio was associated with a smaller fetal head circumference, length and weight from third trimester onwards, leading to a smaller size at birth (differences for birth head circumference -0.08 SD (95% CI -0.15 to -0.01); birth length -0.09 SD (95% CI -0.16 to -0.02) and birth weight (-0.18 SD (95% CI -0.24 to -0.12) per SD increase in fetal U/C ratio). The differences were smaller during childhood but remained significant. At the age of 6, a higher third trimester fetal U/C ratio was associated with smaller head circumference (difference -0.05 SD (95% CI -0.11 to 0), height (difference -0.12 SD (95% CI -0.17 to -0.06), weight (difference -0.12 SDS (95% CI -0.17 to -0.06)) and body mass index (difference -0.06 SDS (95% CI -0.12 to -0.01). We observed significant interactions between sex and repeated measured head circumference in fetal - and childhood models and fetal length ($P < 0.05$). The differences tended to be stronger in boys than in girls. The associations of fetal blood flow redistribution with growth patterns remain relatively constant over time. We did observe an overall association of fetal blood flow redistribution with growth, but no significant interaction between fetal flow and (gestational) age were present. The associations of third trimester fetal umbilical artery PI and cerebral artery PI separately with longitudinal fetal and childhood growth patterns are given in the Supplementary Material (Figure S2). The associations of third trimester fetal umbilical artery PI with longitudinal growth patterns tended to be similar as those for the fetal U/C ratio (Figure S2). The associations of third trimester cerebral artery PI with longitudinal growth patterns are given in Figure S3 and showed a non-significant tendency for a positive association of third trimester higher cerebral artery PI with head circumference, height and weight growth during fetal life and childhood, with smaller differences at older ages (Figure S3). The associations of third trimester fetal U/C ratio with childhood growth patterns in the groups of children in the lowest and highest third trimester

estimated fetal weight categories are given in the Supplementary Material (Figures S4 and S5). Children in the lowest 10 percent of third trimester estimated fetal weight group tended to have a stronger inverse association of third trimester fetal U/C ratio with head circumference, height and weight growth during fetal life and childhood, with larger differences at older ages compared with growth patterns in total group. Children in highest 10 percent of third trimester estimated fetal weight group showed similar longitudinal growth patterns compared the total group.

Third trimester fetal flow distribution and childhood adiposity outcomes

Table 3 showed that third trimester fetal umbilical artery PI, middle cerebral artery PI or the U/C ratio were not associated with, total fat mass, lean mass, android/gynoid fat mass ratio or preperitoneal fat area at the age of 6.

Discussion

Main findings

In this population-based prospective cohort study we observed that third trimester fetal blood flow redistribution, with a preferential fetal blood flow to brain cerebral circulation at the expense of lower body parts, was associated with increased risks of adverse birth outcomes. Also, fetal blood flow redistribution was associated with a smaller third trimester fetal head circumference, length, and weight growth from third trimester onwards with persistent effects until the age of 6 years. We did not observe associations of third trimester fetal blood flow redistribution with childhood total body and abdominal fat measures.

Strengths and limitations

The main strength of this study is the large population-based cohort studied from fetal life onwards. To our knowledge, thus far this is the largest study, which examined the effects of fetal blood flow distribution on early growth trajectories. The population-based setting enabled us to assess the fetal blood flow measures across the full range, rather than only in fetuses with growth restriction or other complications. Follow-up measurements at the age of 6 were available in 75% of the children. Missing growth and fat distribution measurements could lead to selection bias and loss of power. Our results would be biased if the associations between fetal blood flow distribution and growth outcomes 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.

Interpretation

Fetal growth and development largely depends on an adequate placental and fetal circulation.(1) An adverse intra-uterine environment with reduced oxygenation or nutrition levels in the developing fetus leads to fetal blood flow redistribution, an important fetal adaptation mechanism to ensure blood transport to the most important organs.(2, 3) The first signs of a suboptimal intra-uterine environment can be detected in a decline in umbilical vein blood flow. A compensatory increase in ductus venosus diameter increases the blood flow to the heart.(4, 5) This will be followed by an increase in the umbilical artery blood

flow resistance and a decrease in cerebral artery resistance.(32) Both the umbilical and uterine artery blood flow parameters provide information about the placental circulation, but assessment of vascular resistance in the umbilical artery may be more closely related to the fetal condition. Umbilical artery Doppler resistance indices were related to fetal levels of glucose and amino acids(33), and therefore the umbilical artery PI could be used as substitute measurement of placenta function.(34) In line with previous studies from the same cohort(17, 18) 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.

Several studies have shown that placental insufficiency is related to increased risks of adverse birth outcomes.(35–37) However, Akolekar et al. showed that at 35–37 weeks of gestation the association of a low CPR with adverse birth outcomes is weak.(38) Mechanisms that cause preterm birth were not clearly defined.(39) We hypothesized that it might be that a suboptimal fetal circulation causes fetal undernutrition and subsequently results in preterm delivery.(40) In the current study, we observed that small variations in third trimester fetal umbilical artery PI, middle cerebral artery PI and the U/C ratio, in a low risk population, were associated with increased risks of preterm birth and small-size for gestational age at birth. These observations suggest measuring the middle cerebral artery PI and the U/C ratio, in addition to placental pulsatility indices, may be useful for identifying fetuses at risk of adverse birth outcomes.

Studies have shown that fetal blood flow redistribution in late pregnancy results in asymmetrical fetal growth restriction characterized by a relatively larger head size than body size at birth.(7–9) Previously, we observed that third trimester uterine, fetal umbilical and cerebral blood flow measures are correlated with a lower estimated fetal weight.(11) However, not much is known about fetal blood flow redistribution and the consequences on childhood growth. We have previously shown that an increased third trimester umbilical artery vascular resistance is associated with lower fetal, infant and childhood growth.(12) Thus far, it is not known whether only umbilical artery flow changes or also cerebral artery flow changes affect childhood growth and body fat distribution. Results from the longitudinal growth analyses in the current study showed that a higher third trimester U/C ratio and umbilical artery PI were associated with persistently lower head circumference, length, and weight growth from third trimester until 6 years. The associations of third trimester cerebral artery PI with longitudinal growth patterns tended to have smaller effect estimates compared with third trimester umbilical artery PI and the U/C ratio. Our results among children with low third trimester estimated fetal weight and high third trimester estimated fetal weight suggest that the effects of third trimester U/C ratio on childhood growth patterns may be stronger among children with a lower third trimester estimated fetal weight. However, the confidence intervals were wide and the observed differences in effect estimates were not significant. Further studies are needed to explore whether combining fetal growth and U/C ratio may help to identify children at risk for long term health outcomes.

In our study, we did not find evidence for full catch up growth following small-size at birth in response to fetal blood flow distribution. These findings suggest that fetal blood flow

distribution leads to persistently smaller size during fetal life and childhood. Previous studies have shown that a low birth weight is associated with increased fat measures at different ages.(10, 41, 42) The underlying pathways may include differences in body proportions, which subsequently predispose individuals to increased risks of cardiovascular disease in later life.(35, 43–45) Previously, in a larger group of our cohort, we observed small associations of higher umbilical placental PI with increased total fat mass and the android/gynoid fat mass ratio in childhood.(12) However, our study did not suggest any effect of fetal blood flow redistribution on childhood overweight and fat mass measures, which might be due to the smaller study sample. Also, it might be that the consequences of a suboptimal fetal environment might not be detectable in early childhood, but might become more evident in later life. Further studies are needed to identify the long-term consequences of fetal blood flow redistribution on growth patterns and adiposity measures in young adulthood.

The umbilical artery PI reflects the fetal-placental connection, whereas the middle cerebral artery PI reflects the fetal response. The U/C ratio detects the redistribution of fetal blood flow due to adaptations in these two vascular units.(34) Animal models have demonstrated that the ratio is better correlated with fetal hypoxia than the umbilical or the cerebral component by itself.(46) It has also been shown that using the U/C ratio, the MCA/uterine artery or the MCA/umbilical artery, improves the prediction of adverse pregnancy outcomes compared to its individual components.(47) In line with these studies, we observed the strongest associations of the U/C ratio with longitudinal growth analyses from third trimester fetal life until the age of 6 years. However, although our findings suggest that fetal blood flow redistribution increased the risks of adverse birth outcomes and affects a child's growth trajectory, the effect estimates were small and likely to be without direct clinical consequences for individuals.

Conclusion

In this study we observed that third trimester fetal blood flow redistribution with a preferential fetal blood flow to the brain cerebral circulation at the expense of lower body parts, is associated with increased risks of adverse birth outcomes and growth restriction from fetal life onwards. Direct clinical consequences are limited, however our findings are important from an etiological point of view. Follow-up studies to health consequences in adulthood of suboptimal fetal blood flow circulation are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The Generation R Study is being conducted by the Erasmus Medical Center and Erasmus University Rotterdam in close collaboration with the Municipal Health Service Rotterdam area, Rotterdam and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond, Rotterdam. We gratefully acknowledge the contributions of children and their parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam.

Funding

The Generation R Study receives financial support from the Erasmus University Medical Center, Rotterdam and The Netherlands Organization for Health Research and Development (ZonMw). Additionally, we received funding from the European Union's Seventh Framework Programme (FP7/2007-2013), project EarlyNutrition under grant agreement n°289346 and an unrestricted grant from Danone Nutricia Research. Vincent Jaddoe received an additional grant from the Netherlands Organization for Health Research and Development (NWO, ZonMw-VIDI 016.136.361) and an European Research Council Consolidator Grant (ERC-2014-CoG-648916). These sponsors had no role in design and conduct of the study, analysis and interpretation of the data, and preparation, review or approval of the manuscript.

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Figure 1. Associations of third trimester fetal flow redistribution with growth characteristics

Associations of third trimester fetal U/C ratio with fetal and childhood growth characteristics. Values reflect regression coefficients (95% Confidence Interval) and reflect differences in (gestational) age adjusted SDS of growth characteristics per SDS change in U/C ratio. Models are adjusted for age at third trimester. Total group analyses were additionally adjusted for child's sex. P-value of the interaction term of fetal flow with (gestational) age was not significant. P-value for sex interaction <0.01 for model focused on head circumference and prenatal length.

Table 1

Subject characteristics (N=1,195)

Child characteristics	
Third trimester fetal characteristics	
Gestational age at measurement, wk	30.3 (28.5, 32.6)
Umbilical artery pulsatility index	0.97 (0.16)
Middle cerebral artery pulsatility index	1.97 (0.33)
Umbilical/Middle cerebral artery ratio	0.50 (0.11)
Fetal head circumference, cm	28.6 (1.2)
Fetal femur length, cm	5.7 (0.3)
Estimated fetal weight, g	1630 (268)
Birth characteristics	
Gestational age at birth, wk	40.3 (35.9, 42.4)
Head circumference, cm	34.0 (1.6)
Birth weight, g	3514 (540)
Birth length, cm	50.5 (2.3)
Preterm, %	4.7 (56)
Small for gestational age, %	3.7 (44)
Boys, %	52.1 (622)
Childhood characteristics	
Age at follow up, y	5.9 (5.7, 6.6)
Head circumference, cm	51.4 (1.4)
Height, cm	119.0 (5.2)
Weight, kg	22.6 (3.2)
Body mass index, kg/m ²	15.9 (1.4)
Total fat mass, %	23.8 (4.5)
Lean mass, %	72.6 (4.4)
Android/gynoid fat mass ratio, %	23.7 (16.1, 37.8)
Preperitoneal fat area, cm ²	0.37 (0.17, 0.89)

Values are means (standard deviation), medians (95% range), or numbers (%). Non-imputed subject characteristics can be found in Supplementary Material Table S1, infant growth characteristics in Table S2 and maternal characteristics in Table S3.

Table 2

Associations of third trimester fetal umbilical and cerebral blood flow with risks of adverse birth outcomes (N = 1,195)

	Preterm	Small for gestational age
	Odds Ratios (95% CI)	Odds Ratios (95% CI)
Basic model		
Umbilical artery pulsatility index	1.06 (0.80, 1.41)	2.25 (1.65, 3.06) [†]
Middle cerebral artery pulsatility index	0.66 (0.50, 0.87) [†]	1.01 (0.74, 1.37)
Umbilical/Middle cerebral artery ratio	1.42 (1.09, 1.83) [†]	1.62(1.22, 2.14) [†]
Confounder model		
Umbilical artery pulsatility index	1.02 (0.77, 1.37)	2.18 (1.59, 2.99) [†]
Middle cerebral artery pulsatility index	0.65 (0.49, 0.87) [†]	1.01 (0.74, 1.38)
Umbilical/Middle cerebral artery ratio	1.41 (1.08, 1.85) [†]	1.63 (1.21, 2.19) [†]

Values are Odds Ratios (95% Confidence Interval) from logistic regression models that reflect the risk of preterm and small for gestational age at birth per SDS change in third trimester fetal umbilical and cerebral blood flow. Basic model is adjusted for gestational age at third trimester and child's sex. Confounder model is additionally adjusted for maternal age, parity, educational level, body mass index, smoking, folic acid supplementation use and pregnancy complications.

* P-value <0.05

[†] P-value <0.01

Table 3

Associations of third trimester fetal umbilical and cerebral blood flow with body fat distribution at the age of 6 (N = 923)

	Fat mass, %	Lean mass, %	Android/gynoid fat mass ratio	Preperitoneal fat area (cm ²)
Basic model				
Umbilical artery pulsatility index	0.26 (-0.02, 0.53)	-0.26 (-0.53, 0.01)	-0.01 (-0.39, 0.37)	0.01 (-0.03, 0.04)
Middle cerebral artery pulsatility index	0.18 (-0.09, 0.45)	-0.19 (-0.44, 0.07)	-0.05 (-0.41, 0.32)	0.01 (-0.02, 0.04)
Umbilical/Middle cerebral artery ratio	-0.00 (-0.28, 0.28)	0.00 (-0.27, -0.27)	-0.02 (-0.37, 0.39)	-0.01 (-0.04, 0.02)
Confounder model				
Umbilical artery pulsatility index	0.20 (-0.07, 0.47)	-0.20 (-0.46, 0.05)	-0.11 (-0.49, 0.27)	-0.00 (-0.04, 0.03)
Middle cerebral artery pulsatility index	0.11 (-0.15, 0.37)	-0.12 (-0.37, 0.13)	-0.13 (-0.49, 0.24)	0.01 (-0.02, 0.04)
Umbilical/Middle cerebral artery ratio	0.05 (-0.23, 0.32)	-0.04 (-0.31, 0.22)	0.03 (-0.35, 0.41)	-0.01 (-0.04, 0.02)

Values are regression coefficients (95% Confidence Interval) from linear regression models that reflect differences in childhood body fat distribution per SDS change in third trimester fetal umbilical and cerebral blood flow. Basic model is adjusted for gestational age at third trimester, estimated fetal weight, child's sex and current age. Confounder model is additionally adjusted maternal age, parity, educational level, body mass index, smoking, folic acid supplementation use and pregnancy complications. Preperitoneal fat area was log transformed. Models with fat mass and lean mass were additionally adjusted for length of the child at age 6.