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Fetal–placental blood flow and neurodevelopment in childhood: population-based neuroimaging study

S. SAMMALLAHTI[1,2], H. TIEMEIER[1,2], S. LOUWEN[1,3], E. STEEGERS[4], M. HILLEGERS[1], V. W. V. JADDOE[5] and T. WHITE[1]

[1]*Department of Child and Adolescent Psychiatry and Psychology, Erasmus University Medical Center, Rotterdam, The Netherlands;* [2]*Department of Social and Behavioral Sciences, Harvard School of Public Health, Boston, MA, USA;* [3]*Department of Neuroscience, Erasmus University Medical Center, Rotterdam, The Netherlands;* [4]*Department of Obstetrics and Gynecology, Erasmus University Medical Center, Rotterdam, The Netherlands;* [5]*Department of Pediatrics, Erasmus University Medical Center, Rotterdam, The Netherlands*

CONTRIBUTION

What are the novel findings of this work?
We used a population-based sample of 2803 mother–child dyads to investigate fetal determinants of neurodevelopment in a general population. Increased placental vascular resistance, measured using prenatal Doppler ultrasound, is associated with poorer motor and cognitive abilities at 4–12 years of age.

What are the clinical implications of this work?
Fetal–placental blood flow may impact long-term brain development. While these effects may be subtle at population level, future research should consider possible long-term effects when designing and evaluating early interventions.

ABSTRACT

Objective *Antenatal Doppler measurements of the fetal umbilical and cerebral circulations can predict perinatal complications; however, it is unclear if subtle variations in antenatal Doppler measurements are associated with long-term neurodevelopmental outcome. In this study, we examined whether antenatal Doppler measurements of the fetal–placental circulation are associated with cognitive and motor abilities and brain morphology in childhood.*

Methods *To evaluate differences in long-term sequelae across the continuum of the umbilical and cerebral artery circulations in the general population, we utilized a population-based longitudinal cohort study approach. In women from the Generation R study, we measured second- and third-trimester umbilical artery pulsatility index (UA-PI). Children underwent non-verbal intelligence testing at 4–8 years of age, and at 8–12 years they underwent finger-tapping tests to measure fine motor skills, balance beam tests to measure gross motor skills and brain magnetic resonance imaging. We assessed the relationships between prenatal UA-PI and neurodevelopmental outcome using linear regression. We adjusted for child age and sex, maternal age, education, parity and smoking status.*

Results *The study sample included 2803 pregnancies. Higher third-trimester UA-PI was associated with poorer fine motor performance (0.41 (95% CI, 0.11–0.70) fewer taps on the finger-tapping test per 1 SD higher UA-PI) and gross motor performance (0.64 (95% CI, 0.20–1.08) fewer steps on the balance beam test per 1 SD higher UA-PI). One SD higher third-trimester UA-PI was also associated with 0.65 (95% CI, 0.04–1.25) points lower intelligence quotient; however, unlike the associations with motor abilities, this finding did not persist after correction for multiple testing. Higher second-trimester UA-PI was associated with smaller brain volume (6.1 (95% CI, 1.0–11.3) cm³ reduction per 1 SD higher UA-PI), but the association did not persist after correction for multiple testing.*

Conclusion *Higher placental vascular resistance may have mild adverse effects on neurodevelopmental outcome at school age. While these effects are subtle at population level, we encourage future research into the role of early circulation in brain development. This information*

Correspondence to: Dr S. Sammallahti, Erasmus Medical Center, Department of Child and Adolescent Psychiatry and Psychology, 2060, 3000CB Rotterdam, The Netherlands (e-mail: sara.sammallahti@helsinki.fi)

ORIGINAL PAPER

could be used to develop targeted interventions. © 2020 *The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

The fetal–placental circulation delivers nutrients and oxygen during a critical period of fetal brain development. While the perinatal risks of suboptimal fetal–placental circulation have been recognized, associations with long-term neurodevelopment remain unclear[1,2].

Doppler ultrasound is widely used to quantify the fetal–placental circulation. Umbilical artery (UA) pulsatility index (PI) increases when placental vascular resistance increases (downstream of the fetal circulation). The cerebroplacental ratio (CPR), i.e. the ratio between cerebral- and UA-PI, decreases when blood flow is redistributed to prioritize vital organs. Both markers are associated with perinatal morbidity and death[3–6], and are used to target interventions in high-risk pregnancies[1,7].

Studies on fetal–placental blood flow and long-term neurodevelopmental outcome are scarce. In high-risk pregnancy, UA Doppler predicts developmental delay[8–11] and motor development[10–13] at 1–2 years of age, while follow-up studies among 4–9-year-olds reported no association with intelligence quotient (IQ)[14–16]. In low-risk pregnancy, high UA-PI was found to be associated with poorer memory function at 12 years of age; differences in general reasoning or academic achievement, albeit in the same direction, were not statistically significant[17]. Evidence from large prospective population-based studies is lacking; while costly, the benefit of these studies is that they are ideally suited for identifying risk factors for adverse long-term consequences in a general population, as well as in the presence of confounders.

The aim of this study was to examine whether second- and third-trimester UA-PI and third-trimester CPR are associated with cognitive function at 4–8 years of age and motor function and brain morphology at 8–12 years. The study sample comprises 2803 mother–child dyads from the prospective population-based Generation R study[18,19]. We hypothesized that higher UA-PI and lower CPR are associated with poorer cognitive and motor performance and reduced brain volume, even among individuals whose estimated fetal weight (EFW) is within the normal range.

METHODS

Participants

This study was conducted within the prospective population-based Generation R study[18,19]. Briefly, all women living in Rotterdam, The Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate. We excluded twin pregnancies and stillbirths or perinatal/neonatal deaths. We also excluded women who did not undergo first-trimester (< 14 weeks' gestation) ultrasound for pregnancy dating[20]. We did not use second- or third-trimester ultrasound data for pregnancy dating because we adjusted UA-PI for gestational age and wanted to ensure that gestational-age estimates were affected minimally by individual fetal growth trajectories (which are associated with UA-PI and neurodevelopment). In addition, we excluded randomly one sibling per sibling pair if the mother was recruited more than once (during different pregnancies). In line with a population-based approach, participants were not excluded based on health-related factors; these were addressed using multivariate statistical approaches and sensitivity analyses, as described in Models and covariates.

The Medical Ethical Committee of the Erasmus Medical Center approved the study. Written informed consent was obtained from all adult participants and legal guardians of participating children. Personnel administering follow-up assessments were blinded to fetal data.

Fetal ultrasound

Three trained sonographers performed ultrasound examinations during the second and third trimesters (at ~20 and ~30 weeks, respectively)[21]. Pulsed Doppler was used to measure UA-PI (difference between systolic and diastolic flow velocities per time-averaged velocity) during fetal apnea, without fetal movements, in a free-floating loop of the umbilical cord. The average of three consecutive uniform waveforms was recorded and residualized for gestational age at assessment (UA-PI decreases physiologically as pregnancy progresses).

In a subgroup that volunteered for more detailed assessment[18], third-trimester ultrasound also included measurement of fetal middle cerebral artery (MCA) PI and anterior cerebral artery (ACA) PI[21]. CPRs for ACA (CPR_A) and MCA (CPR_M) were calculated (as ACA-PI or MCA-PI, respectively, divided by UA-PI) and residualized for gestational age.

Gestational age was based on first-trimester ultrasound at a mean gestational age of $12 + 2$ (range, $5 + 4$ to $13 + 6$) weeks[22]. We used crown–rump length for pregnancy dating up to $12 + 4$ weeks ($n = 1614$) and biparietal diameter at $12 + 5$ to $13 + 6$ weeks ($n = 1189$)[20]. EFW during the second- and third-trimester ultrasound examinations (for sensitivity analyses) was calculated using Hadlock's formula[23,24].

Cognitive function (4–8-year follow-up)

Child IQ was estimated using two subtests (mosaics, categories) of the Dutch non-verbal intelligence test, Snijders-Oomen Niet-Verbale Intelligentietest[25], developed to assess reliably many cognitive domains without relying on language skills[25,26]. Raw scores were converted into IQ estimates using normative data tailored to exact age. Estimates ≤ 50 ($n = 7$) and ≥ 150 ($n = 1$) were assigned to 50 and 150, respectively, as the test is not designed to differentiate reliably between individuals beyond these limits.

Motor function (8–12-year follow-up)

Gross motor skills and balance were assessed using the walking backwards task from the Body Co-ordination Test for Children (Körperkoordinationstest für Kinder)[27,28]. This test battery is considered an easy-to-administer, reliable, non-sport-specific test of motor skills; it is used widely in Europe to identify neurodevelopmental and brain injury-related motor problems, and has been validated among school-age Dutch children[27,28]. Children walked backwards on three 3-m long, 5-cm high beams of different widths (6, 4.5 and 3 cm). After a practice trial on the widest beam, each child walked backwards twice along each beam, starting with the widest and finishing with the narrowest[29]. As an outcome, we used the total number of correct steps (until the child stepped off or reached a maximum of eight steps per trial) across all six trials.

Motor control and fine motor speed were assessed using a computerized finger-tapping task. Finger tapping is one of the most frequently used neuropsychological instruments[30], and shows good psychometric properties, including validity in identifying the presence of brain lesions and a range of motor dysfunctions[31]. The test included five trials; participants were asked to tap their index finger as fast as possible for 10 s, in the order: (i) right hand, (ii) left hand, (iii) both hands (alternating), (iv) right hand and (v) left hand[29]. As an outcome, we used the average number of taps across all trials.

Magnetic resonance imaging (8–12-year follow-up)

As described previously[29,32], magnetic resonance images were acquired using the same sequence and scanner (3 Tesla GE 750w Discovery; GE Healthcare, Milwaukee, WI, USA). Following three-plane localizer scans, a high-resolution T1-weighted inversion recovery fast spoiled gradient recalled sequence was acquired ($T_R = 8.77$ ms, $T_E = 3.4$ ms, $T_I = 600$ ms, flip angle $= 10°$, field of view $= 220 \times 220$ mm, acquisition matrix $= 220 \times 220$, slice thickness $= 1$ mm, number of slices $= 230$). Freesurfer v.6.0.0 (http://surfer.nmr.mgh.harvard.edu/) was used to obtain total brain volume (TBV), global cortical and subcortical gray matter (GM), cerebral white matter (WM), cerebellar volume and total intracranial volume[29,32]. Upon visual inspection, low-quality data and participants with incidental findings (e.g. large cysts that could bias the interpretation of magnetic resonance imaging (MRI) results, confirmed by a neuroradiologist) were excluded[29,32].

Models and covariates

In Model 1 (M1), we adjusted for child age during follow-up (years) and sex (male/female). In Model 2 (M2), we added maternal parity (nulliparous or parous, from midwife/hospital records), age at enrolment (years), education (tertiary or lower, self-reported at enrolment) and smoking status (no smoking during pregnancy, smoked until pregnancy was known or continued smoking during pregnancy (including infrequent smoking after pregnancy was known), self-reported prospectively) as potential confounders, based on theoretical expectations[33–37]. An additional model (Model 3 (M3)) included the M2 covariates and the regional brain volumes were residualized for total intracranial volume (outcomes were not residualized in other models).

For sensitivity analyses, we obtained maternal hypertensive disorder diagnoses during pregnancy (chronic or pregnancy-induced hypertension, pre-eclampsia and HELLP syndrome) from midwife/hospital registries.

Statistical analysis

We used separate multiple linear regression models to test the associations between the two primary exposures (second- and third-trimester UA-PI) and the four primary outcomes (IQ, balance beam score, finger-tapping score and TBV). We imputed 50 datasets using multiple imputation by chained equations (MICE) to handle missing covariate data, under the assumption that data were missing at random given the observed values[38]. We used false-discovery rates (FDR; $\alpha = 0.05$) to correct for multiple testing (across eight primary models).

As supplementary outcomes, we investigated global cortical GM, subcortical GM, cerebral WM and cerebellar volumes. As supplementary exposures, we investigated CPR_A and CPR_M.

For sensitivity analyses, we (i) excluded women diagnosed with a hypertensive disorder and those without such data; (ii) stratified the sample into small-for-gestational age (SGA, EFW $< 10^{th}$ percentile) vs non-SGA at the time of Doppler assessment; and (iii) replaced the standardized UA-PI values with raw (non-standardized) UA-PI measures. To determine if any statistically significant associations ($P < 0.05$) were driven by outlier UA-PI values (> 3 SD above or below the mean), we reran the models after excluding these values. Non-linearity was assessed by visual inspection and by including a quadratic term in the primary models.

For non-response analyses, available outcome, exposure and covariate data of those lost to follow-up were compared to those of the analytical sample using independent t-tests, Mann–Whitney U-tests and χ^2 tests.

We used R 3.3.2 (www.r-project.org) and IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA) for analyses.

RESULTS

Among the 8879 recruited pregnant women, we excluded 97 twin pregnancies, 138 stillbirths or perinatal/neonatal deaths, 4376 pregnancies that did not undergo first-trimester ultrasound for pregnancy dating and 180 siblings from sibling pairs (in which the same mother was recruited twice during different pregnancies). Figure 1 describes loss to follow-up. The study sample included 2803 children (68.6% of 4088 eligible for inclusion), of whom 2462 (60.2%) had cognitive

data (6-year follow-up) and 2246 (54.9%) had motor and 1418 (34.7%) had MRI data (10-year follow-up).

Table 1 shows the characteristics of the sample. Second- and third-trimester UA-PI measurements were correlated moderately ($r = 0.31$; $P < 0.001$; $n = 2129$ pregnancies with measurements at both timepoints). Compared to those lost to follow-up ($n = 1285$; Figure 1), women in the analytical sample ($n = 2803$) were older (mean maternal age, 30.4 *vs* 28.7 years; $P < 0.001$), more often nulliparous (60% *vs* 55%; $P = 0.002$), more often had tertiary education (51% *vs* 36%; $P < 0.001$) and smoked less during pregnancy (17% *vs* 22%; $P < 0.001$) and the child was more often female (52% *vs* 47%; $P = 0.002$). Table S1 shows a comparison of imputed *vs* observed covariate data.

Cognitive function

Higher UA-PI was associated with slightly poorer performance on the intelligence test. In M1, effect sizes were small; non-verbal IQ was 0.98 (95% CI, 0.33–1.63) and 0.86 (95% CI, 0.23–1.48) points lower per 1 SD higher second-trimester and third-trimester UA-PI, respectively (Figure 2). In M2, effect sizes and statistical significance were somewhat weaker (Figure 2). Approximately one-tenth of the variance in child IQ was explained by UA-PI, child age and gender, maternal age, parity, education and smoking status ($R^2 = 0.10$ for both the second- and third-trimester models; M2).

Motor function

Higher UA-PI during late gestation was associated with poorer performance on the motor tests. In M1, effect sizes were small; per 1 SD higher UA-PI during the third trimester, participants achieved 0.77 (95% CI, 0.32–1.21) fewer steps in the balancing task and tapped 0.36 (95% CI, 0.07–0.65) fewer times during the finger-tapping test (Figure 2). Additional adjustments (M2) had little effect on these associations. Associations
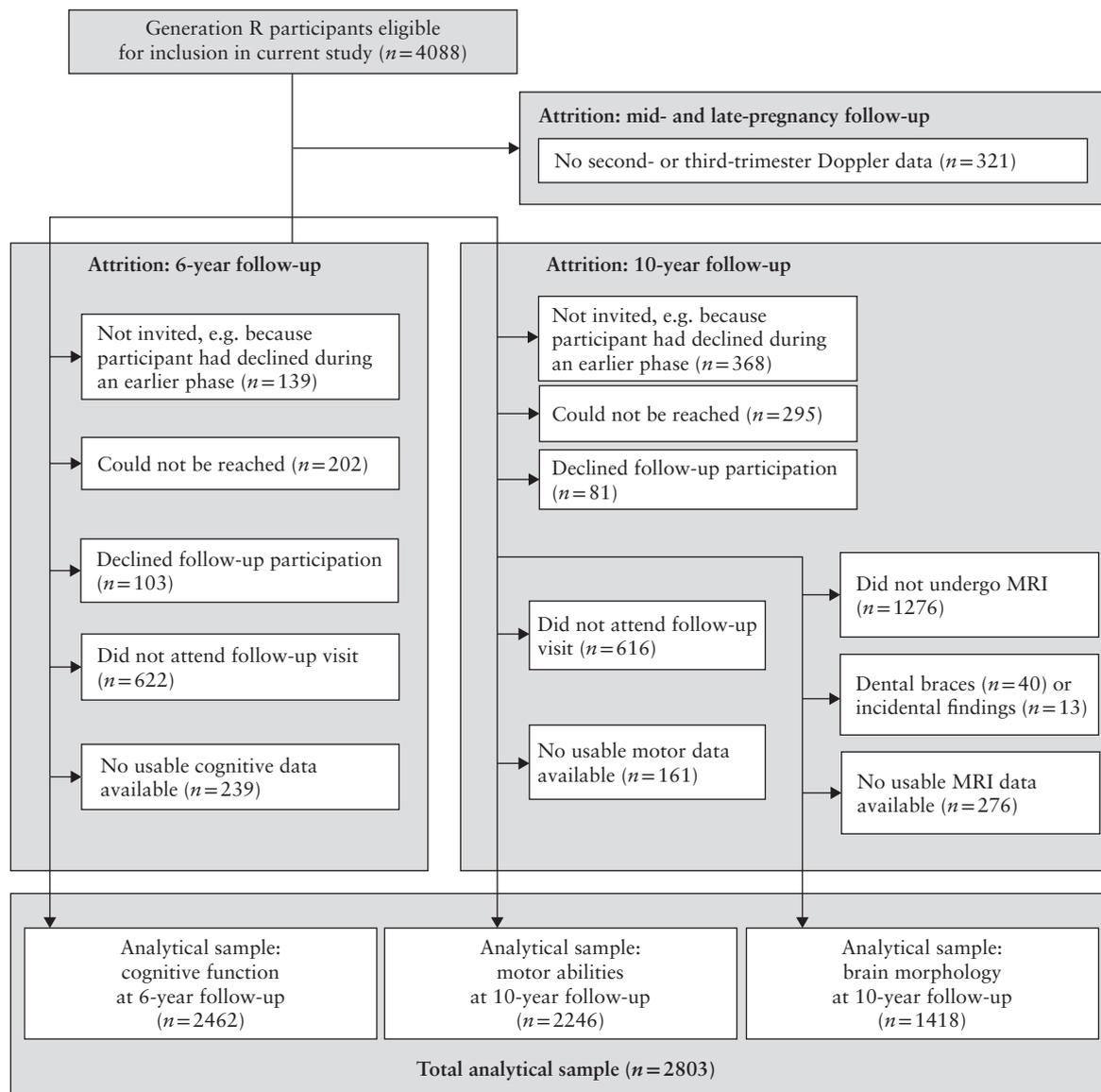

Figure 1 Flowchart summarizing inclusion of study population. MRI, magnetic resonance imaging.

Table 1 Characteristics of the total analytical sample of 2803 pregnancies

Variable	n	Value
Maternal age (years)	2803	30.4 ± 4.7 (16.8 to 43.8)
Nulliparous	2784	1670 (60.0)
Smoking during pregnancy		
None	2504	1832 (73.2)
Until pregnancy known	2504	251 (10.0)
Continued in pregnancy	2504	421 (16.8)
Tertiary education	2670	1364 (51.1)
Hypertensive disorder*	2756	202 (7.3)
Second-trimester US		
GA (weeks)	2406	$20 + 3 \pm 0 + 6$ ($18 + 0$ to $24 + 6$)
UA-PI		
Raw score	2406	1.2 ± 0.2 (0.6 to 2.0)
SD score†	2406	0.0 ± 1.0 (-3.7 to 4.2)
Third-trimester US		
GA (weeks)	2526	$30 + 2 \pm 0 + 6$ ($27 + 1$ to $33 + 4$)
UA-PI		
Raw score	2526	1.0 ± 0.2 (0.5 to 1.9)
SD score†	2526	0.0 ± 1.0 (-2.7 to 5.5)
CPR_A		
Raw score	549	1.9 ± 0.4 (1.0 to 3.6)
SD score†	549	0.0 ± 1.0 (-2.0 to 4.0)
CPR_M		
Raw score	600	2.1 ± 0.5 (0.9 to 4.1)
SD score†	600	0.0 ± 1.0 (-2.4 to 4.0)
Female neonate	2803	1453 (51.8)
GA at birth (weeks)	2803	39.9 ± 1.7 (26.3 to 43.3)
Birth weight (kg)	2799	3.4 ± 0.5 (0.7 to 5.1)
Cognitive testing		
Age (years)	2462	6.1 ± 0.4 (4.9 to 8.8)
Non-verbal IQ (points)	2462	102 ± 15 (50 to 150)
Motor testing		
Age (years)	2246	9.8 ± 0.3 (8.6 to 11.9)
Balance-beam score (steps)	1679	27 ± 8.4 (3 to 48)
Finger-tapping score (taps)		
Average	2036	39 ± 6.4 (11 to 64)
Dominant hand	2036	42 ± 6.0 (10 to 62)
Non-dominant hand	2036	38 ± 5.3 (14 to 59)
Alternating	2036	36 ± 13 (2 to 87)
MRI		
Age (years)	1418	10.1 ± 0.6 (8.8 to 12.0)
Brain volume (cm³)		
Total	1418	1214 ± 109 (857 to 1592)
Cortical GM	1418	582 ± 53 (404 to 774)
Subcortical GM	1418	61 ± 4.5 (46 to 76)
Cerebral WM	1418	425 ± 48 (291 to 600)
Cerebellum	1418	145 ± 13 (96 to 190)

Data are presented as mean $\pm$ SD (range) or *n* (%). *Hypertensive disorders, based on medical records, included pregnancy-induced hypertension ($n = 123$), pre-eclampsia or HELLP syndrome ($n = 53$), superimposed pre-eclampsia or HELLP syndrome ($n = 8$) and pre-existing hypertensive disorder ($n = 18$). †6.0%, 5.0%, 7.1% and 6.5% of participants, respectively, had second- and third-trimester umbilical artery pulsatility index (UA-PI) and third-trimester CPR_A and CPR_M ≥ 1.645 SD above the mean (corresponding to the 95th percentile cut-off for the normal distribution), while 3.8%, 3.9%, 2.2% and 2.0% of participants, respectively, had values ≥ 1.645 SD below the mean (corresponding to the 5th percentile). CPR_A, cerebroplacental ratio calculated by dividing the PI of the anterior cerebral artery by that of the UA; CPR_M, cerebroplacental ratio calculated by dividing the PI of the middle cerebral artery by that of the UA; GA, gestational age; GM, gray matter; IQ, intelligence quotient; MRI, magnetic resonance imaging; US, ultrasound; WM, white matter.

between second-trimester UA-PI and motor outcome were weaker, and effect estimates for balancing and finger-tapping performance were approximately half the third-trimester estimates (M2). Approximately 3–5% of the variance in the results of the balancing ($R^2 = 0.03$ and 0.04 for second and third trimester, respectively) and finger-tapping ($R^2 = 0.04$ and 0.05, respectively) tests was explained by the M2 variables.

Brain morphology

Higher UA-PI was associated with slightly smaller brain volume in childhood. One SD higher UA-PI during the second and third trimesters was associated with 7.2 (95% CI, 1.9–12.4) cm³ and 5.9 (95% CI, 0.7–11.2) cm³ lower TBV, respectively (M1) (Figure 2). In M2, these effect estimates were reduced to 6.1 and 4.6 cm³, respectively. Approximately 30% of TBV variance was explained in the second-trimester ($R^2 = 0.31$) and third-trimester ($R^2 = 0.30$) models (M2).

Associations between UA-PI and brain morphology were not tissue-specific; rather, small overall reductions across cortical GM, subcortical GM, WM and the cerebellum were observed (Table S2). Most effect estimates were slightly larger and statistically more significant for second- compared to third-trimester UA-PI; however, their 95% CIs had substantial overlap and the associations did not survive adjustment for total intracranial volume (M3), supporting a lack of tissue specificity (Figure 2 and Table S2).

Correction for multiple testing

Of the statistically significant associations between UA-PI and cognitive and motor function and TBV ($P < 0.05$; M2), only those of third-trimester UA-PI with finger tapping and balance performance persisted after FDR correction (Figure 2); those between second-trimester UA-PI and TBV and between third-trimester UA-PI and IQ did not persist.

Sensitivity analysis

Exclusion of women with hypertensive disorders ($n = 202$) and of those without such data ($n = 47$) had no robust effect on the associations of UA-PI with cognitive or motor function or TBV (Table S3).

Effect estimates for IQ, finger tapping and TBV were larger among SGA compared with non-SGA children, while the 95% CIs were wider, as expected due to the smaller group size (Table S4). Among non-SGA children, higher third-trimester UA-PI was associated with poorer performance on motor tasks, and higher second-trimester UA-PI was associated with smaller TBV (M2; Table S4).

Associations between non-standardized UA-PI and neurodevelopmental outcome are shown in Table S5; the results remained similar.

(a) Non-verbal IQ (points)

(b) Balancing performance (steps)

(c) Finger tapping (taps)

(d) Total brain volume (cm³)

Figure 2 Effect of umbilical artery pulsatility index (UA-PI) during the second and third trimesters on non-verbal intelligence quotient (IQ) at 6-year follow-up (a), and balancing (b) and finger-tapping (c) performance and total brain volume (d) at 10-year follow-up. The effect estimate represents the change in estimated non-verbal IQ (IQ points) (a), balance performance (total number of backward steps on balance beams across six trials) (b), finger-tapping test performance (average number of taps per 10-s period, across five trials) (c) or change in total brain volume (cm³) (d), per 1 SD higher UA-PI. Model 1 was adjusted for the child's age during follow-up and the child's sex. Model 2 was adjusted for Model-1 covariates and maternal age, parity, smoking during pregnancy and education. *Association persisted after correction for multiple testing of fully adjusted models (Model 2). SDS, standard deviation score (residualized for gestational age at measurement).
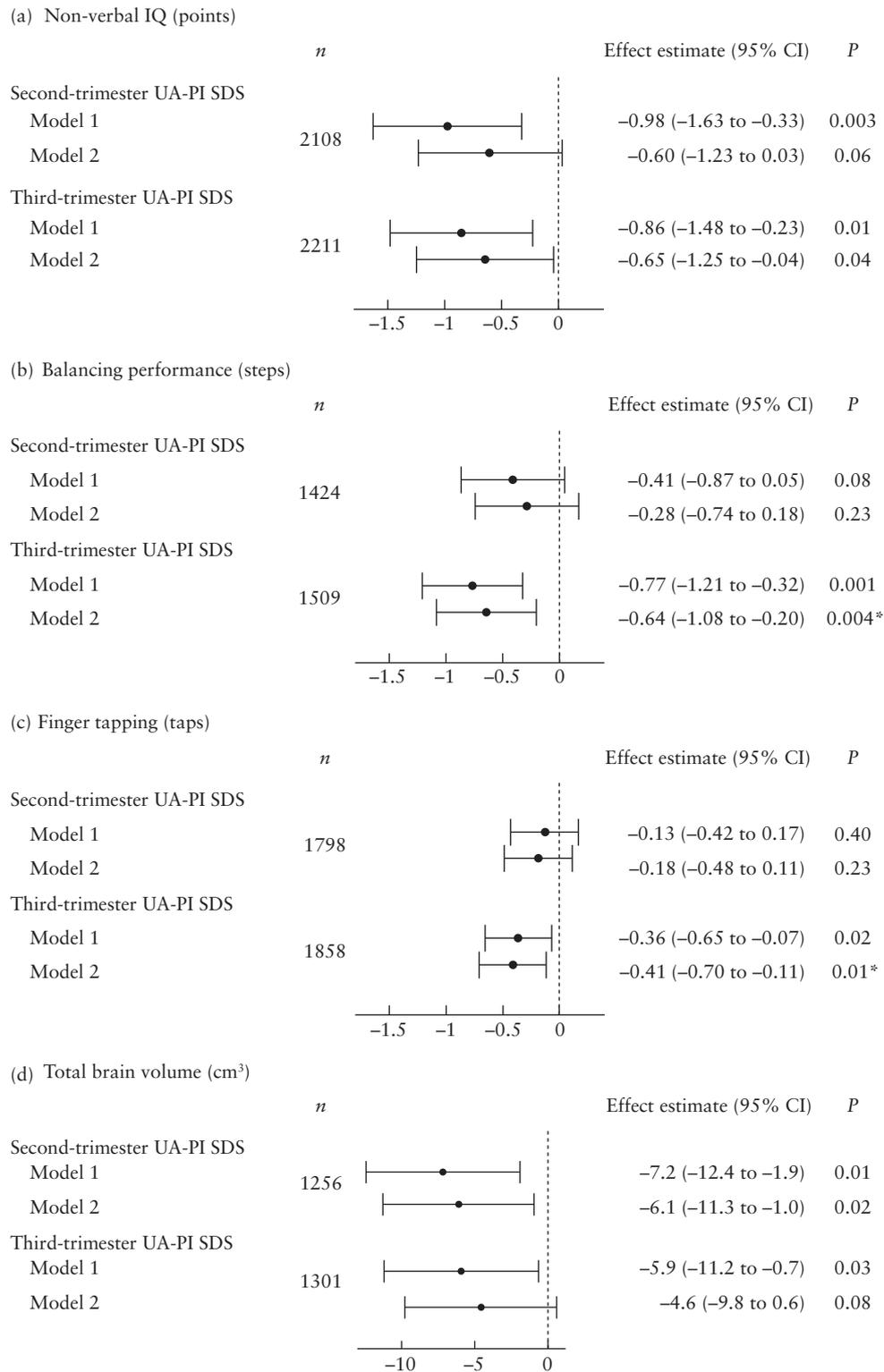
Of the statistically significant associations between UA-PI and cognitive and motor function and TBV ($P < 0.05$; M2), only those of UA-PI with balancing ($P = 0.005$) and finger tapping ($P = 0.01$) persisted after excluding extreme UA-PI values (> 3 SD above or below the mean; $n = 15$ during the second trimester and $n = 17$ during the third trimester), while those with IQ and TBV were borderline significant ($P = 0.08$ and 0.05, respectively) (Figure S1). We found no evidence of non-linearity (quadratic term P-values > 0.23).

Cerebroplacental ratio

In the subgroup in which third-trimester CPR was assessed ($n = 602$), CPR was not associated with IQ, balancing or TBV (P-values > 0.07; M2; Table S6). One SD higher in CPR_M was associated with 0.71 (95% CI, 0.12–1.29) more taps on the finger-tapping test; this was driven by UA-PI ($P = 0.04$), while MCA-PI was not associated with finger tapping ($P = 0.60$).

DISCUSSION

In this population-based study of 2803 children, increased placental vascular resistance was associated with adverse neurodevelopmental outcome at 4–12 years of age. These associations were explained only partly by maternal socioeconomic status, age, parity and smoking status.

Third-trimester UA-PI was associated with subtle differences in fine motor and gross motor abilities at 8–12 years of age. Consistent with this, some studies have reported an association between UA Doppler and motor development at 1–2 years ($n = 172–484$)[10–13]; however, others found no such association[8,9,39], perhaps due to study design differences or smaller samples ($n = 82–218$).

Third-trimester UA-PI was associated with non-verbal IQ at 4–8 years. Some studies with much smaller sample sizes ($n = 25–180$) reported that UA Doppler did not predict verbal or non-verbal IQ at 4–12 years[14–17]; their negative findings could be related to insufficient power. However, in this study, associations with IQ showed more confounding by maternal background characteristics and were less robust to FDR, as compared to associations with motor function; replication is needed to confirm our finding.

With regard to outcome specificity, we advise caution, as the timing (and possibly sensitivity) of the motor/cognitive assessments differed. While some brain regions central to motor function may be more vulnerable to early hypoxia than others[40], we found no tissue-specific differences at 8–12 years of age. If anything, higher UA-PI was associated with smaller brain volume overall.

UA Doppler is recommended in high-risk pregnancy in which false positives and unnecessary interventions are less likely[1,7]. Severely compromised fetal–placental circulation often leads to fetal growth restriction, and increased vascular resistance is also associated with maternal hypertensive disorders and placental dysfunction[1,2,7].

However, poor placental perfusion may also lead to perinatal complications even among seemingly normally grown fetuses[41]. Our effect estimates were mostly larger among SGA cases, yet associations were present even among non-SGA and non-hypertensive participants.

The magnitude of the estimated effects of prenatal factors on neurodevelopmental outcome were, understandably, very small; these outcomes are influenced by a myriad of environmental and genetic factors and were measured up to 12 years after the exposure. Per 1 SD increase in third-trimester UA-PI, motor and cognitive performance scores were approximately 0.04–0.08 SD poorer. Such small effects are not relevant directly for guiding clinical decision-making; however, identifying even subtle population-level effects can be meaningful if they point to preventable causes of key long-term adversity[42,43]. The main message of this study is that suboptimal fetal–placental circulation may affect neurodevelopment, and these effects may be long-lasting. Thus, to identify pregnancies in which the fetus has an increased risk of neurodevelopmental problems, to design targeted antenatal interventions and to decide how to support high-risk mothers and children after birth, we should take into account that increased placental vascular resistance may have long-lasting neurodevelopmental implications, in addition to immediate perinatal risks.

Contrary to our hypothesis, dilation of cerebral arteries to prioritize vital organs, i.e. brain sparing, did not explain our findings. The lack of robust associations with CPR was somewhat surprising. Previously, we found within the Generation R study that redistribution of blood flow, both to the ACA and MCA, was associated with behavioral problems at 18 months, as evaluated by the mother[44]. Among high-risk cases, brain sparing was associated with delayed neurodevelopment at 2–5 years[8,45–47], but not with cognitive ability or behavioral problems at 11–12 years[48,49] or motor performance at 11 years of age[50]. The inherent plasticity of the developing brain could explain why some neurodevelopmental differences become less evident over time, and repeated-measure outcome designs could elucidate the role of plasticity.

Based on our results, UA-PI at ~30 weeks, compared to at ~20 weeks, may be more predictive of later cognitive and motor ability. During the early third trimester, the brain undergoes rapid development and differentiation, and may be especially vulnerable to hypoxic–ischemic WM injury, which is important in the development of neuromotor dysfunction[51–53]. Furthermore, the effect of abnormal vascular architecture and obliteration of terminal villi on placental perfusion often becomes evident during the early third trimester[54,55].

Strengths and limitations

The strengths of this study include the large sample, repeat second- and third-trimester UA Doppler measurements, diverse neurodevelopmental data, prospective design and

long follow-up. Inherent limitations include possible residual confounding and attrition, which could affect generalizability (probably to more disadvantaged populations) and (under) estimation of effect magnitude. While using pooled estimates from multiple imputation models partly addresses selective attrition and estimation uncertainty, it assumes data are missing at random given all observed values; this assumption cannot be tested, and its violation could lead to biased estimates. Most previous studies have examined extreme waveforms, e.g. absent/reversed end-diastolic flow among high-risk populations, or used somewhat arbitrary cut-offs, such as the 90th or 95th percentile, to classify PI values into normal and abnormal; our results expand on these findings by examining PIs along a continuum within the general population, the benefits of which include increased power and external validity. On the other hand, our population-based approach may also be a limitation. In clinical samples, the risk of developmental delay could be driven by severe circulatory abnormalities and major complications (e.g. intellectual disability); in our population, these cases may be too rare to cause a discernible signal or even lost due to attrition. The prognosis for fetuses with severely compromised fetal–placental circulation was thus beyond the scope of this study; a clinical sample enriched in such cases would be better suited for this purpose. Furthermore, though of interest, we could not assess memory function or mediation of functional outcomes through morphology, perinatal complications or iatrogenic prematurity due to lack of data/robustness and temporal overlap; future studies should evaluate the role of factors such as perinatal morbidity, which may lie on the causal pathway.

Conclusions

Increased placental vascular resistance may lead to adverse neurodevelopmental outcome at school age. We encourage further research into how fetal–placental blood flow affects the brain. This information could be used to develop targeted interventions to optimize long-term neurodevelopment.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Scatterplots showing the statistically significant associations between umbilical artery pulsatility index (UA-PI) and neurodevelopmental outcomes ($P < 0.05$), with the linear regression line shown in blue and extreme UA-PI values in black.

Table S1 Comparison between observed values and imputed data within the full analytical sample

Tables S2–S4 Association between pulsatility index of the umbilical artery during the second and third trimesters and cortical gray matter, subcortical gray matter, cerebral white matter and cerebellar volumes during the 10-year follow-up (Table S2), non-verbal intelligence quotient, motor performance and total brain volume in childhood (Tables S3 and S4), among participants whose mothers were not diagnosed with a hypertensive disorder during pregnancy (Table S3) and who were small-for-gestational age (estimated fetal weight $< 10^{th}$ percentile) *vs* those who were not (estimated fetal weight $\geq 10^{th}$ percentile) at the time of the Doppler ultrasound assessment (Table S4)

Tables S5 and S6 Association between raw pulsatility index scores (not standardized for gestational age) of the umbilical artery during the second and third trimesters (Table S5) or cerebroplacental ratios of the anterior and middle cerebral arteries during the third trimester (Table S6) and non-verbal intelligence quotient, motor performance and total brain volume in childhood