

ORIGINAL RESEARCH

Maternal Cardiovascular Health in Early Pregnancy and Childhood Brain Structure

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BACKGROUND: Poor cardiovascular health during pregnancy has been associated with adverse neurocognitive outcomes in the offspring. We examined the associations of maternal cardiovascular health factors with brain structure in 10-year-old children.

METHODS AND RESULTS: We included 2797 mother–offspring pairs from the Generation R Study. Maternal body mass index, gestational weight gain, blood pressure, insulin, glucose, and lipid blood concentrations were obtained in early pregnancy. Childhood structural brain measures, including global metrics of brain tissue volumes and white matter microstructure, were quantified by magnetic resonance imaging at 10 years. As compared with offspring of mothers with normal weight, those of mothers with underweight had smaller total brain volume (difference, -28.99 [95% CI -56.55 to -1.45] cm^3). Similarly, as compared with offspring of mothers with gestational weight gain between the 25th and 75th percentile, those of mothers with gestational weight loss or no gestational weight gain (<25th percentile), had smaller total brain volume (difference, -13.07 [95% CI, -23.82 to -2.32] cm^3). Also, higher maternal diastolic blood pressure in early pregnancy was associated with lower offspring white matter mean diffusivity (difference, -0.07 [95% CI, -0.11 to -0.02] SD score). After multiple testing correction, only the association of maternal diastolic blood pressure with lower offspring white matter mean diffusivity remained statistically significant. No associations were observed of maternal insulin, glucose, and lipid concentrations with childhood brain outcomes.

CONCLUSIONS: Our findings suggest that maternal cardiovascular health during pregnancy might be related to offspring brain development in the long term. Future studies are needed to replicate our findings and to explore the causal nature of the associations.

Key Words: blood pressure ■ brain structure ■ cardiovascular health ■ mothers ■ offspring

Cardiovascular disease is a major public health problem and is the leading cause of mortality and morbidity in the general adult population worldwide.¹ In particular, an adverse cardiovascular health status in pregnant women may lead to pregnancy complications and have long-term consequences for the offspring.^{2–4} A suboptimal intrauterine environment, attributable to adverse maternal cardiovascular risk factors, can lead to placental dysfunction, inflammation and changes in various metabolic processes, potentially altering fetal brain development, which may subsequently influence brain health in later life.^{5–7} The existing literature suggests that adverse maternal body fat measures and cardiovascular

risk factors during pregnancy can potentially affect brain development, behavior, and cognition in children. For example, maternal obesity, hypertension, and diabetes during pregnancy have been associated with adverse neurodevelopmental and cognitive outcomes in offspring, including lower intelligence, executive functioning, developmental delay, and mental and behavioral disorders.^{8–17} Also, a growing body of evidence suggests that not only offspring exposed to maternal obesity but offspring of mothers with underweight may have impaired intellectual development.^{18–20} To the contrary, a prospective study among 5191 mother–offspring pairs from the ALSPAC (Avon Longitudinal Study of Parents

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Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.026133>

For Sources of Funding and Disclosures, see page 9.

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CLINICAL PERSPECTIVE

What Is New?

- Suboptimal cardiovascular health status of mothers in early pregnancy, before the onset of clinically manifest cardiovascular disease, might be related to offspring brain development in the long term.
- Higher maternal diastolic blood pressure in early pregnancy is associated with differences in white matter microstructure in offspring aged 10 years.
- Lower maternal body mass index and weight gain in early pregnancy tended to be associated with offspring smaller brain volumes.

What Are the Clinical Implications?

- This study shows an association of an adverse cardiovascular health profile during early pregnancy with offspring brain morphology at 10 years.
- While this is an observational study and causality cannot be inferred, the current findings in combination with prior literature may inform health care providers to focus on cardiovascular risk prevention in women already in early pregnancy.

Nonstandard Abbreviations and Acronyms

AD	axial diffusivity
ALSPAC	Avon Longitudinal Study of Parents and Children
DTI	diffusion tensor imaging
FA	fractional anisotropy
MD	mean diffusivity
SDS	SD scores

and Children) cohort suggested a positive association of gestational weight gain with better cognitive outcomes in offspring.²¹ Though some previous studies have focused on neurocognitive outcomes, the associations of maternal cardiovascular risk factors with offspring brain structure were rarely explored. A previous neuroimaging study showed that offspring of pregnancies complicated by preeclampsia, as compared with offspring of uncomplicated pregnancies, exhibited enlarged brain regional volumes of the cerebellum, temporal lobe, and amygdala at ages 7 to 10 years.²² In addition to brain structural changes, a functional magnetic resonance imaging (MRI) study among 91 children aged 7 to 11 years suggested an association between children exposed to gestational diabetes and increased hypothalamic blood flow in response to glucose.²³ Studies performed thus far have

mainly focused on maternal clinically manifest diseases and do not allow for clear conclusions about the associations of maternal body fat measures and cardiovascular risk factors with offspring brain development. Recent results from our own research group, the Generation R Study, showed that higher maternal prepregnancy body mass index (BMI) was associated with differences in white matter microstructure in offspring aged 10 years.²⁴ In the current study, we aimed to extend previous findings including several cardiovascular risk factors as well as focusing on early pregnancy as a sensitive period since it largely reflects maternal fat deposition and cardiovascular profile and, to a lesser extent, growth changes of the fetus, placenta, and uterus, which mostly occurs in mid and late pregnancy.²⁵

Therefore, in this large population-based cohort study of 2797 mother–offspring pairs, we investigated the associations of maternal cardiovascular health factors, including BMI; gestational weight gain; blood pressure; and insulin, glucose, and lipid concentrations in early pregnancy with childhood brain structure at age 10 years. We used a hierarchical approach that involved global measures of brain volume and white matter microstructure without defining specific regions of interest, as there was no a priori hypothesis.

METHODS

The data, analytic methods, and study materials will not be made available readily to other researchers for purposes of reproducing the results or replicating the procedure because of legal and informed-consent restrictions. However, they are available from the corresponding author upon reasonable request.

Study Design

This study was embedded in the Generation R Study, a population-based prospective cohort from early pregnancy onward. Approval was obtained from the Medical Ethics Committee of Erasmus Medical Center, Rotterdam, the Netherlands (MEC 198.782/2001/31), and the procedures followed were in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all participants.²⁶ Pregnant women were enrolled between April 2002 and January 2006. In total, 5706 mothers and their singleton children attended the study visit at 10 years, of whom information about maternal cardiovascular health factors in early pregnancy was available in 5169 subjects. Next, we excluded 1696 children who did not participate in the neuroimaging assessment and an additional 676 children without sufficient quality of neuroimaging data. The final population for analysis comprised 2797 mother–offspring pairs with

structural MRI and 2645 with useable diffusion tensor imaging (DTI) outcomes (for flowchart see Figure S1).

Early Pregnancy Cardiovascular Health Factors

Maternal cardiovascular health factors were all measured in early pregnancy (gestational age, 13.1 weeks [95% range, 9.8–17.4]) and included information on maternal BMI, gestational weight gain, and blood pressure and nonfasting insulin, glucose, total cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations.²⁷

Maternal BMI (kg/m²) in early pregnancy was calculated from height and weight, both measured without shoes and heavy clothing. Maternal BMI was categorized into clinical categories according to World Health Organization cutoffs (underweight [<18.5 kg/m²], normal weight [18.5 – 24.9 kg/m²], overweight [25.0 – 29.9 kg/m²], and obesity [≥ 30.0 kg/m²]).²⁸ Gestational weight gain in early pregnancy was calculated as the difference between weight at enrollment and prepregnancy weight obtained by questionnaire.²⁹ We divided weight gain by gestational age to obtain the weight gain per week.³⁰ Further, we categorized gestational weight gain per week into <25 th percentile (ranging from weight loss to 0 weight gain), between the 25th and 75th percentile (ranging from 0.007 to 0.286 kg/wk), and >75 th percentile (weight gain >0.286 kg/wk). Blood pressure was measured in the right upper arm, in sitting position, with the validated Omron 907 automated digital oscillometric sphygmomanometer (OMRON Healthcare Europe B.V., Hoofddorp, the Netherlands) by well-trained staff. Systolic and diastolic blood pressure were averaged from 2 measurements with a 1-minute interval.³¹ Insulin, glucose, total cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations were measured from nonfasting blood samples. Sample processing and storage procedures have been previously described.³²

Brain Imaging at 10 Years

Brain scans were obtained on a single 3-Tesla scanner (General Electric MR750w, Milwaukee, WI) using the same sequence protocol for all children. Following a 3-plane localizer scan, a high-resolution 3-dimensional T1-weighted scan was acquired with an inversion recovery fast-spoiled gradient recalled sequence (parameters: repetition time=8.77 ms, echo time=3.4 ms, inversion time=600 ms, flip angle=10°, field of view=220 mm×220 mm, acquisition matrix=220×220, slice thickness=1 mm, number of slices=230).³³ Images were processed using FreeSurfer version 6.0 (<http://surfer.nmr.mgh.harvard.edu/>).³⁴ The quality of FreeSurfer output was visually inspected, and images with artifacts and insufficient quality were excluded.

Global metrics of volume, including total brain volume, total gray matter volume, and total white matter volume were extracted.

DTI outcomes were obtained using an echo-planar sequence with 3 $b=0$ scans and 35 diffusion-weighted images ($b=1000$ s/mm²) with the parameters: repetition time=12500 ms, echo time=72.8 ms, field of view=240 mm×240 mm, acquisition matrix=120×120, slice thickness=2 mm, and number of slices=65. DTI data were processed with the FMRIB Software Library and the Camino diffusion MRI toolkit.^{35,36} The diffusion tensor was fit at each voxel, and common scalar metrics including global fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity were computed. FA describes the degree of anisotropic diffusion and is highly sensitive to microstructural changes, and MD describes the average diffusion in all directions.^{37,38} White matter tracts were determined using fully automated probabilistic fiber tractography.^{37,39} Average FA and MD were calculated for each tract. Diffusion image quality was assessed by manual and automated inspection.

Covariates

Information on maternal age, ethnicity, educational level, parity, smoking habits, alcohol consumption, and folic acid supplement use was obtained by questionnaires during pregnancy. Maternal psychopathology, particularly pregnancy-specific anxiety, was assessed by an adapted version of the Pregnancy Outcome Questionnaire at around 12 weeks of gestation.^{40,41} Child sex and date of birth, from which age at neuroimaging assessment was calculated, were available from medical records.

Statistical Analysis

A nonresponse analysis was performed to test for potential differences in baseline characteristics between participants and nonparticipants using Pearson's chi-square tests, independent sample *t*-tests, and Mann-Whitney tests. We assessed the associations of maternal cardiovascular health factors in early pregnancy with childhood global volumetric measures including total brain, total gray matter and total white matter volume, and overall white matter microstructure measures using linear regression analyses. Nonlinearity of the relationship was assessed using generalized additive models. Since the associations of maternal BMI and gestational weight gain with brain outcomes in 10-year-old children were not linear, we present the results for the BMI categories (underweight, normal weight, overweight, and obesity) and gestational weight gain categories (<25 th percentile, between 25th and 75th percentiles, and >75 th percentile). For all analyses, we present a basic model

including child's sex and age at outcome measurements, and a confounder-adjusted model, which additionally included maternal age, ethnicity, educational level, parity, pregnancy-specific anxiety, smoking habits, alcohol consumption, and folic acid supplement use. Gestational weight gain and blood pressure models were also adjusted for maternal prepregnancy BMI and maternal height, respectively. Potential confounders were represented in a directed acyclic graph (Figure S2) and were selected on the basis of previous literature and by observing a >10% change in effect estimate.^{12,24} We did not adjust for any birth outcomes (eg, gestational age or birth weight), as these factors might be an intermediate in the causal pathway of the investigated associations, which could lead to biased results.⁴²

To enable comparison of effect sizes of different cardiovascular exposure measures, we constructed SD scores (SDSs) ([observed value–mean]/SD). In addition, global white matter microstructure measures were also standardized, and if an association with a DTI metric was observed, we performed a follow-up analysis with AD and radial diffusivity to better describe the underlying microstructural properties. Models with global volumetric measures as outcomes were not standardized because of clinical interpretability in cm³, nor adjusted for intracranial volume, given the high correlation ($r > 0.89$). Based on previous literature, we tested for statistical interactions with child sex in all models, but none of the interaction terms was significant.¹⁸ As sensitivity analyses, we assessed the associations of maternal prepregnancy BMI with offspring brain structure at 10 years.

Missing data in covariates (proportion of missing data ranged from 0% to 13.4%, with the exception of folic acid use [22.3%]) were imputed using Markov chain Monte Carlo approach with use of the fully conditional specification method assuming a nonmonotone missing pattern.⁴³ We created 10 imputed data sets and reported the pooled effect estimates and their 95% CIs. To minimize false-positive findings attributable to multiple testing, we compared each *P* value with a threshold defined as 0.05 divided by the effective number of independent tests estimated on the basis of the correlation between the exposures (*P* value threshold of 0.0076).⁴⁴ We performed all statistical analyses using the Statistical Package of Social Sciences version 25.0 for Windows (IBM, Chicago, IL).

RESULTS

Participant Characteristics

Both participant characteristics and nonresponse analyses are presented in Table 1. Of all pregnant women, 65% had a European ethnic background,

59.3% were nulliparous, and 77.0% never smoked. The nonresponse analyses showed that as compared with mothers of children without brain MRI data available, mothers of children with brain MRI measurements were slightly older, highly educated, reported less anxiety, more often had a normal weight, and gained less weight in early pregnancy.

Early Pregnancy Body Fat Measures and Offspring Brain Structure

The results of the basic model showed an inverse U-shaped relation between maternal BMI and brain global volumetric measures in 10-year-old children. As compared with offspring of mothers with normal weight, those of mothers with lower or higher BMI had smaller total brain and total gray matter volumes (all *P* values <0.05). Also, as compared with offspring of mothers with gestational weight gain between the 25th and 75th percentiles, those of mothers with gestational weight loss or no gestational weight gain had smaller total brain and total gray and total white matter volumes (all *P* values <0.05) (Table S1). After adjustment for potential confounders, only the associations of maternal underweight with smaller offspring total brain and total gray matter volumes (differences, -28.99 [95% CI, -56.55 to -1.45] cm³ and -18.12 [95% CI, -34.12 to -2.12] cm³, respectively) remained significant. Similarly, the associations of maternal gestational weight loss or no gestational weight gain with smaller offspring total brain and total white matter volumes (differences, -13.07 [95% CI, -23.82 to -2.32] cm³ and -6.94 [95% CI, -12.09 to -1.80] cm³, respectively) also remained significant after adjustment for potential confounders. However, after a multiple testing correction, none of these associations remained statistically significant (Table 2). Sensitivity analyses showed similar results (Table S2).

Early Pregnancy Cardiovascular Measures and Offspring Brain Structure

In the basic model, higher maternal insulin was associated with smaller total brain and total gray matter volumes in offspring aged 10 years (all *P* values <0.05). Also, higher maternal high-density lipoprotein cholesterol was associated with larger offspring total gray matter volume and higher white matter FA (all *P* values <0.05) (Table S3). After adjustment for potential confounders, these results attenuated into nonsignificant. In the confounder models, 1 SDS increase in maternal systolic and diastolic blood pressure were associated with lower offspring white matter MD (differences, -0.05 [95% CI, -0.09 to -0.00] SDS and -0.07 [95% CI, -0.11 , -0.02] SDS, respectively). However, after multiple testing correction, only the association of

Table 1. Characteristics of Study Population and Nonresponse Analyses*

	Participants (responders) (N=2797)	Nonparticipants (non-responders) (N=2372)	P value†
Maternal characteristics			
Age, y, mean (SD)	30.8 (4.8)	30.6 (5.0)	<0.05
Ethnicity, n (%)			0.16
European	1786 (65.0)	1460 (63.1)	
Non-European	962 (35.0)	854 (36.9)	
Education, n (%)			<0.01
Primary school	181 (6.8)	213 (9.5)	
Secondary school	1084 (40.8)	988 (44.3)	
Higher education	1390 (52.4)	1030 (46.2)	
Parity, n (%)			<0.05
Nulliparous	1648 (59.3)	1322 (56.1)	
Folic acid use, n (%)			<0.01
Yes	1737 (79.9)	1333 (74.6)	
Alcohol consumption, n (%)			<0.05
Yes	1238 (50.6)	992 (47.6)	
Smoking, n (%)			<0.05
Never	1926 (77.0)	1574 (74.4)	
Until pregnancy was known	224 (9.0)	184 (8.7)	
Continued during pregnancy	350 (14.0)	358 (16.9)	
Pregnancy-specific anxiety, score, mean (SD)	0.8 (0.4)	0.9 (0.4)	<0.05
Height, cm, mean (SD)	168.1 (7.3)	167.4 (7.5)	<0.01
Prepregnancy weight, kg, mean (SD)	66.4 (12.5)	66.4 (12.1)	0.96
Prepregnancy BMI, kg/m ² , median (95% range)	22.5 (18.0–34.8)	22.7 (18.2–34.3)	<0.05
Gestational age in early pregnancy, wks, median (95% range)	13.1 (9.8–17.4)	13.4 (9.9–17.5)	<0.01
Weight in early pregnancy, kg, mean (SD)	69.4 (13.0)	69.5 (12.4)	0.73
BMI, kg/m ² , median (95% range)	23.6 (18.8–35.7)	23.9 (18.9–35.6)	<0.01
BMI categories, n (%)			<0.05
Underweight	55 (2.0)	38 (1.6)	
Normal weight	1736 (62.4)	1394 (59.0)	
Overweight	696 (25.0)	651 (27.6)	
Obesity	294 (10.6)	278 (11.8)	
Weight gain in early pregnancy, kg/wk, mean (SD)	0.16 (0.2)	0.18 (0.2)	<0.05
Weight gain in early pregnancy categories, n (%)			<0.01
<25th percentile	521 (28.3)	399 (25.4)	
25th–75th percentile	861 (46.7)	704 (44.8)	
>75th percentile	460 (25.0)	468 (29.8)	
Systolic blood pressure, mmHg, mean (SD)	115.7 (11.9)	115.2 (12.0)	0.18
Diastolic blood pressure, mmHg, mean (SD)	67.9 (9.4)	68.0 (9.3)	0.57
Insulin, pmol/L, median (95% range)	113.1 (19.8–627.1)	114.7 (19.7–623.0)	0.83
Glucose, mmol/L, mean (SD)	4.4 (0.8)	4.4 (0.9)	0.15
Total cholesterol, mmol/L, mean (SD)	4.8 (0.9)	4.8 (0.9)	0.89
HDL cholesterol, mmol/L, mean (SD)	1.8 (0.3)	1.8 (0.4)	0.15
Triglycerides, mmol/L, median (95% range)	1.3 (0.7–2.7)	1.3 (0.6–2.7)	0.26
Child characteristics			
Sex, N (%)			0.92
Girls	1415 (50.6)	1196 (50.4)	

(Continued)

Table 1. Continued

	Participants (responders) (N=2797)	Nonparticipants (non-responders) (N=2372)	P value†
Age at MRI, y, mean (SD)	10.1 (0.6)	10.2 (0.8)	<0.01

BMI indicates body mass index; HDL, high-density lipoprotein; and MRI, magnetic resonance imaging.

*Values are means (SD), medians (95% range), or numbers of subjects (valid %).

†P values for differences in subject characteristics between groups were calculated performing independent sample t-tests for normally distributed continuous variables, Mann–Whitney test for nonnormally distributed continuous variables, and chi-square tests for categorical variables.

maternal diastolic blood pressure with lower offspring white matter MD remained statistically significant. A follow-up analysis showed that higher maternal systolic and diastolic blood pressure were associated with lower offspring white matter AD and maternal diastolic blood pressure were additionally associated with lower radial diffusivity (all *P* values <0.05) (Table S4). No associations were observed between maternal glucose, total cholesterol, and triglyceride concentrations and any of the offspring brain outcomes (Table 3).

DISCUSSION

In this population-based prospective cohort study, higher maternal diastolic blood pressure in early pregnancy was associated with lower global white matter MD in offspring aged 10 years. Our findings also suggest that as compared with offspring of mothers with normal weight, those of mothers with underweight tended to have smaller total brain and total gray matter volumes. Similarly, maternal gestational weight loss or

no gestational weight gain in early pregnancy tended to be associated with smaller offspring total brain and total white matter volumes.

Interpretation of Main Findings

Poor cardiovascular health profiles of mothers during pregnancy have been associated with suboptimal neurodevelopment outcomes in the offspring.^{5,7} In early pregnancy, human brain development begins with the differentiation of the neural progenitor cells, and by the end of the embryonic period the rudimentary structures of the brain and central nervous system are already established.⁴⁵ During this ongoing complex process, fetal brain growth and development occur rapidly; thus, adverse exposures during this period may have long-term consequences for child brain development.

A UK birth cohort among 11 025 five-year-old children and 9882 seven-year-old children showed that maternal prepregnancy BMI was negatively associated with children's cognitive performance.⁹ Similarly, previous studies have suggested an association

Table 2. Maternal Body Fat Measures in Early Pregnancy and Childhood Brain Structure at 10 Years

Maternal body fat measures	Global volumetric measures (cm ³)			Global white matter microstructure measures (SDS)	
	Total brain volume	Total gray matter	Total white matter	Fractional anisotropy	Mean diffusivity
BMI categories (N=2781)					
Underweight (N=55)	-28.99 (-56.55 to -1.45)*	-18.12 (-34.12 to -2.12)*	-10.85 (-24.08 to 2.38)	-0.08 (-0.43 to 0.27)	0.19 (-0.16 to 0.54)
Normal weight (N=1736)	Reference	Reference	Reference	Reference	Reference
Overweight (N=696)	-5.38 (-14.53 to 3.78)	-3.43 (-8.75 to 1.89)	-1.94 (-6.34 to 2.46)	-0.02 (-0.13 to 0.09)	0.01 (-0.10 to -0.12)
Obesity (N=294)	0.31 (-12.75 to 13.36)	-2.56 (-10.14 to 5.02)	2.85 (-3.42 to 9.12)	-0.00 (-0.16 to 0.01)	-0.05 (-0.21 to 0.11)
Gestational weight gain categories (N=1842)					
<25th percentile (N=521)	-13.07 (-23.82 to -2.32)*	-6.09 (-12.36 to 0.18)	-6.94 (-12.09 to -1.80)†	-0.07 (-0.21 to 0.06)	0.03 (-0.10 to 0.16)
25th–75th percentile (N=861)	Reference	Reference	Reference	Reference	Reference
>75th percentile (N=460)	-4.50 (-15.79 to 6.80)	-5.20 (-11.78 to 1.38)	0.69 (-4.71 to 6.10)	-0.02 (-0.16 to 0.12)	0.02 (-0.12 to 0.16)

Values are linear regression coefficients (95% CIs) and reflect the change in cm³ of childhood brain global volumetric and in SD scores of global white matter microstructure measures for maternal cardiovascular risk factors in standard deviation scores. Models are adjusted for child sex and age at the neuroimaging assessment and maternal age; ethnicity; educational level; parity; pregnancy-specific anxiety; and smoking, alcohol, and folic acid use during pregnancy. Gestational weight gain models are additionally adjusted for maternal prepregnancy BMI. BMI indicates body mass index; and SDS, SD score.

**P*<0.05.

†*P*<0.01.

Table 3. Maternal Cardiovascular Risk Factors During Pregnancy and Childhood Brain Outcomes at 10 Years

Maternal cardiovascular risk factors (SDS)	Global volumetric measures (cm ³)			Global white matter microstructure measures (SDS)	
	Total brain volume	Total gray matter	Total white matter	Fractional anisotropy	Mean diffusivity
Systolic blood pressure (N=2777)	1.42 (−2.40 to 5.25)	0.35 (−1.89 to 2.57)	1.08 (−0.77 to 2.92)	0.02 (−0.03 to 0.07)	−0.05 (−0.09 to −0.00)*
Diastolic blood pressure (N=2777)	−2.25 (−6.03 to 1.52)	−1.76 (−3.95 to 0.44)	−0.50 (−2.32 to 1.32)	0.01 (−0.04 to 0.06)	−0.07 (−0.11 to −0.02)†‡
Insulin (N=2113)	−3.18 (−7.56 to 1.20)	−2.55 (−5.11 to 0.00)	−0.62 (−2.71 to 1.47)	−0.01 (−0.06 to 0.05)	−0.03 (−0.09 to 0.02)
Glucose (N=2114)	−2.61 (−6.90 to 1.68)	−1.78 (−4.29 to 0.72)	−0.82 (−2.87 to 1.23)	−0.04 (−0.10 to 0.01)	0.02 (−0.04 to 0.07)
Total cholesterol (N=2144)	0.64 (−3.69 to 4.97)	0.19 (−2.34 to 2.71)	0.44 (−1.64 to 2.51)	0.04 (−0.02 to 0.09)	−0.03 (−0.09 to 0.02)
HDL cholesterol (N=2145)	−0.68 (−5.11 to 3.76)	−0.32 (−2.90 to 2.26)	−0.38 (−2.49 to 1.74)	0.03 (−0.03 to 0.08)	−0.01 (−0.07 to 0.04)
Triglycerides (N=2142)	1.31 (−3.09 to 5.71)	1.11 (−1.45 to 3.68)	0.18 (−1.92 to 2.29)	−0.00 (−0.06 to 0.05)	−0.03 (−0.09 to 0.02)

Values are linear regression coefficients (95% CIs) and reflect the change in cm³ of childhood brain global volumetric and in SD scores of global white matter microstructure measures for maternal cardiovascular risk factors in SD scores. Models are adjusted for child sex and age at the neuroimaging assessment and maternal age; ethnicity; educational level; parity; pregnancy-specific anxiety; and smoking, alcohol, and folic acid use during pregnancy. Systolic and diastolic blood pressure models are additionally adjusted for maternal height. HDL indicates high-density lipoprotein; SDS, SD scores.

**P*<0.05.

†*P*<0.01.

‡These results survived multiple comparison correction.

between prenatal exposure to maternal obesity and higher risk of intellectual disability and lower executive functioning.^{8,10,11} In addition, a recent neuroimaging study including our study group and data from 2 other European birth cohorts showed that maternal prepregnancy BMI was associated with higher FA and lower MD in offspring aged 10 up to 26 years.²⁴ Similarly, maternal underweight has been associated with impaired intellectual development in offspring.^{18,19} Interestingly, results of a longitudinal study showed that both low and high maternal prepregnancy BMI were associated with increased risk of delayed mental development among 2-year-old US children.²⁰ In line with these previous findings, in the current study we found an inverse U-shaped relation between maternal BMI and brain global volumetric measures in offspring aged 10 years. Even when accounting for socioeconomic and lifestyle family factors, the associations of maternal underweight with smaller offspring total brain and total gray matter volumes remained significant. However, after a multiple testing correction, these results attenuated into nonsignificant. We cannot exclude the possibility that our results might have been underpowered to detect differences by maternal underweight because of the small sample size (*n*=55).

Literature on the association between gestational weight gain and offspring neurodevelopment is limited and inconsistent. On the one hand, results of a prospective study from the ALSPAC cohort among 5191 mother–offspring pairs suggested positive associations of gestational weight gain with cognitive development outcomes in offspring aged 4, 8, and 16 years.²¹ On the other hand, other studies reported no association or inverse association between excessive gestational weight gain and offspring cognitive development.^{11,18,46}

In the current study, we focused specifically on weight gain in early pregnancy since it largely reflects maternal fat deposition, whereas gestational weight gain in mid and late pregnancy reflects growth of the fetus, placenta, and uterus. We observed that as compared with offspring of mothers with gestational weight gain between the 25th and 75th percentiles, those of mothers with maternal gestational weight loss or no gestational weight gain tended to have smaller total brain and total white matter volumes in childhood. However, these results should be interpreted with caution as the effect estimates attenuated after multiple testing correction.

Hypertensive disorders of pregnancy, a group of disorders including chronic hypertension, gestational hypertension, and preeclampsia are key risk factors for pregnancy complications and have been associated with offspring suboptimal mental and neurodevelopmental outcomes.^{12–15} A Finnish prospective study among 4743 mother–child pairs showed that maternal preeclampsia increase the risk of childhood behavioral and emotional disorders in offspring from birth up to 10.8 years.¹⁵ Previous DTI studies suggest a link between neurodevelopmental disorders and cognitive abilities and differences in white matter microstructure among children and adolescents.^{47–49} In the present study, we found an association of higher maternal systolic and diastolic blood pressure with lower offspring global white matter MD and AD. However, only the association of maternal diastolic blood pressure remained statistically significant after multiple testing correction. Although the independent associations of systolic and diastolic blood pressure with cerebrovascular outcomes have been previously demonstrated, we cannot exclude the possibility of these specific results being

chance findings.^{50,51} Prior work has demonstrated that higher FA and lower MD are linked to white matter maturation and the opposite linked to pathology.³⁹ Thus, based on these general observations, the association of higher diastolic blood pressure linked to lower MD is counterintuitive. However, several explanations may exist that could explain this finding. First, the diffusion tensor model used in this study is sensitive to complex fiber patterns (eg, crossing fibers). It is possible that in some brain areas, more mature or healthy white matter shows a more complex fiber architecture, which then could manifest as lower FA and higher MD.⁵² Another potential example is related to accelerated maturation, where under stress the brain develops at a faster pace.⁵³ It is important to note that these examples are purely speculative, and, as the current study focused on brain morphology and structural connectivity only, caution is warranted regarding potential functional implications of the observed associations.

Diabetes in pregnancy, including gestational diabetes or pregestational diabetes, have been also associated with increased risk of childhood poorer cognitive outcomes.^{54–56} A previous functional neuroimaging study among 91 children aged 7 to 11 years suggested an association between children exposed to gestational diabetes and increased hypothalamic blood flow in response to glucose, which might predict greater adiposity risk. Moreover, previous studies among women with diabetes also suggested an association between maternal lipid and glucose concentrations during pregnancy and poorer performance of the offspring on IQ tests and motor development assessments.^{16,17} Contrary to previous findings, we did not observe associations of maternal insulin, glucose, and lipid concentrations in early pregnancy with childhood brain structure. A possible explanation for our findings is that subtle differences in maternal metabolic risk factors before the onset of a clinically manifest disease may not trigger detectable structural brain changes in offspring.

Several potential mechanisms could explain the reported association of maternal diastolic blood pressure and differences in offspring white matter microstructure. For example, a suboptimal placental perfusion caused by high blood pressure in pregnancy can lead to reduced oxygen and nutritional supplies, potentially altering ongoing neurodevelopmental processes that start prenatally and continue throughout childhood, such as altered axonal development or myelination, which may subsequently influence brain health in later life.⁵⁷ Other mechanisms include alterations in immune system and hypothalamic–pituitary–adrenal axis functioning. Previous studies showed that altered hypothalamic–pituitary–adrenal axis and immune system functioning were associated with both hypertensive pregnancy disorders and neurodevelopmental outcomes in offspring.^{58–61}

Altogether, the associations of maternal cardiovascular health factors in early pregnancy with brain

structure in offspring aged 10 years were largely explained by socioeconomic and lifestyle family factors. Maternal diastolic blood pressure may, independently of these factors, be associated with differences in offspring white matter microstructure. Although the observed associations are small on an individual level and should be cautiously interpreted, the results may be important from a developmental perspective since adverse exposures during pregnancy may potentially lead to long-term consequences for offspring brain development. Because of the observational design of this study, we cannot infer causality. Further studies are needed to replicate and validate our findings and to further investigate potential causal pathways and underlying mechanisms of these observed associations.

Strengths and Limitations

Study strengths were the prospective, population-based design, the large number of subjects for whom we had detailed information available on maternal measurements and offspring neuroimaging data, and the adjustment for multiple potential confounders. However, this study also has some limitations. First, of all singleton children who attended the study visit at 10 years, 90.6% of their mothers had information on at least 1 measurement of cardiovascular health in early pregnancy. Only 54.1% of the children had neuroimaging data available at 10 years. Nonresponse could lead to selection bias if the associations of maternal cardiovascular health in early pregnancy with offspring brain outcomes differ between those included and excluded in the analyses. As shown in the nonresponse analyses, mothers of children with and without brain MRI data available were different regarding the socioeconomic background, lifestyle characteristics, and cardiovascular health profile. We cannot exclude the possibility of selection bias, but we believe it has little influence on our findings since we adjusted for most of these factors.⁶² Second, we used BMI cutoffs for nonpregnant adults to create the BMI categories in early pregnancy. This might have resulted in a misclassification of BMI. However, similar results were observed after assessing the associations of maternal prepregnancy BMI with childhood brain structure. Also, we relied on a self-reported prepregnancy weight to calculate the gestational weight gain in early pregnancy, which might introduce potential misclassification bias, and subsequently could lead to an underestimation of the observed associations. However, it is likely to be limited because of the good reliability and validity of self-reported prepregnancy weight in representing measured weight.⁶³ Third, weight gain was divided by gestational age to obtain the gestational weight gain per week. While throughout pregnancy weight gain is generally nonlinear, assuming a constant weight

gain in early pregnancy could have influenced our results. However, this is probably not likely as little individual variation in weight gain is expected in the first weeks of pregnancy.⁶⁴ Fourth, we used nonfasting instead of fasting blood samples, which might lead to less precision in the cardiovascular risk factor assessments. Although nonfasting samples are largely used in population-based studies, they may reduce the accuracy of the exposure measurements. Fifth, since the prevalence of mothers with underweight was low in this study population, the power to detect an association may have been more limited because of lower sample sizes. Finally, although we have adjusted for many potential confounders, unmeasured residual confounding might still be present because of the observational design of the study.

CONCLUSIONS

Maternal diastolic blood pressure in early pregnancy was associated with lower global white matter diffusivity in offspring aged 10 years. Our findings also suggest that maternal BMI and gestational weight gain in early pregnancy may be associated with offspring brain volumes. Future studies are needed to assess causality and explore whether these associations link to neurocognitive outcomes.

ARTICLE INFORMATION

Received March 16, 2022; accepted August 29, 2022.

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Acknowledgments

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the Municipal Health Service Rotterdam area, the Rotterdam Homecare Foundation and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR), Rotterdam. We gratefully acknowledge the contribution of the participating children, their parents, general practitioners, hospitals, midwives, and pharmacies in Rotterdam. Silva analyzed the data and wrote the article. Drs Santos, Muetzel, Vernooij, van Rijn, Jaddoe, and El Marroun contributed to the design of the study, analyses, writing the article, interpretation of the data, and revisions and gave input at all stages of the study. All authors approved the final version of the manuscript.

Sources of Funding

The general design of the Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam; the Erasmus University Rotterdam; the Netherlands Organization for Health Research

and Development; the Netherlands Organization for Scientific Research, and the Ministry of Health, Welfare, and Sport. Dr Jaddoe received grants from the European Research Council (ERC-2014-CoG-648916). This project was supported by funding support from the European Union's Horizon 2020 research and innovation program under Grant Agreements No. 733206 (LifeCycle). Dr El Marroun was supported by Stichting Volksbond Rotterdam, the Netherlands Organization for Health Research and Development (Aspasia Grant No. 015.016.056), and the NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation (Grant No. 27853). Dr Muetzel was supported by the Sophia Foundation (S18-20). Supercomputing computations were supported by the Netherlands Organization for Scientific Research Physical Sciences Division: Exacte Wetenschappen, and SURFSara: Cartesius computer cluster [www.surfsara.nl].

Disclosures

None.

Supplemental Material

Tables S1–S4

Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Maternal body fat measures in early pregnancy and childhood brain structure at 10 years, basic models.

Body mass index	Global volumetric measures (cm ³)			Global white matter microstructure measures (SDS)	
	Total brain volume	Total gray matter	Total white matter	Fractional anisotropy	Mean diffusivity
BMI categories (N=2,781)					
Underweight (N=55)	-30.30 (-55.65,-4.95)*	-18.59 (-34.50,-3.68)*	-11.72 (-23.57,0.13)	-0.09 (-0.39,0.22)	0.15 (-0.15,0.45)
Normal weight (N=1,736)	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Overweight (N=696)	-15.95 (-24.25,-7.66)**	-10.63 (-15.51,-5.75)**	-5.32 (-9.19,-1.44)**	-0.06 (-0.16,0.04)	0.01 (-0.08,-0.10)
Obesity (N=294)	-17.58 (-29.24,-5.91)**	-13.87 (-20.73,-7.01)**	-3.73 (-9.18,1.72)	-0.12 (-0.25,0.02)	-0.03 (-0.16,0.11)
Gestational weight gain categories (N=1,842)					
< 25 th percentile (N=521)	-17.80 (-27.92,-7.69)**	-10.42 (-16.39,-4.45)**	-7.35 (-12.07,-2.63)**	-0.09 (-0.21,0.03)	0.04 (-0.07,0.16)
25 th -75 th percentile (N=861)	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
> 75 th percentile (N=460)	-8.89 (-19.43,1.64)	-7.55 (-13.76,-1.33)*	-1.36 (-6.28,3.56)	-0.05 (-0.18,0.07)	-0.00 (-0.12,0.12)

Values are linear regression coefficients (95% confidence intervals) and reflect the change in cm³ of childhood brain global volumetric and in standard deviation scores of global white matter microstructure measures for maternal cardiovascular risk factors in standard deviation scores. Models are adjusted for child sex and age at the neuroimaging assessment. *p < 0.05. ** p < 0.01.

Table S2. Maternal body fat measures in early pregnancy and childhood brain structure at 10 years, sensitivity analyses.

Maternal body fat measures	Global volumetric measures (cm ³)			Global white matter microstructure measures (SDS)	
	Total brain volume	Total gray matter	Total white matter	Fractional anisotropy	Mean diffusivity
BMI categories (N=2,294)					
Underweight (N=96)	-9.27 (-29.98,11.44)	-5.13 (-17.15,6.90)	-4.17 (-14.07,5.73)	-0.10 (-0.36,0.16)	-0.02 (-0.27,0.24)
Normal weight (N=1,615)	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Overweight (N=422)	-1.97 (-12.64,8.71)	-2.10 (-8.30,4.09)	0.13 (-4.99,5.25)	-0.04 (-0.17,0.09)	-0.02 (-0.15,0.11)
Obesity (N=161)	5.57 (-10.51,21.65)	-0.69 (-10.02,8.65)	6.26 (-1.45,13.98)	0.04 (-0.16,0.23)	-0.08 (-0.28,0.12)

Values are linear regression coefficients (95% confidence intervals) and reflect the change in cm³ of childhood brain global volumetric and in standard deviation scores of global white matter microstructure measures for maternal cardiovascular risk factors in standard deviation scores. Models are adjusted for child sex and age at the neuroimaging assessment and maternal age, ethnicity, educational level, parity, pregnancy-specific anxiety and smoking, alcohol and folic acid use during pregnancy. *p < 0.05. ** p < 0.01.

Table S3. Maternal cardiovascular risk factors in early pregnancy and childhood brain structure at 10 years, basic models.

Maternal cardiovascular risk factors (SDS)	Global volumetric measures (cm ³)			Global white matter microstructure measures (SDS)	
	Total Brain volume	Total Gray Matter	Total White Matter	Fractional Anisotropy	Mean Diffusivity
Systolic blood pressure (N= 2,777)	1.63 (-1.85,5.11)	0.58 (-1.47,2.62)	1.05 (-0.59,2.69)	0.01 (-0.03,0.06)	-0.3 (-0.07,0.01)
Diastolic blood pressure (N= 2,777)	-1.26 (-4.69,2.16)	-1.23 (-3.24,0.78)	-0.04 (-1.66,1.58)	0.00 (-0.04,0.04)	-0.4 (-0.08,0.00)
Insulin (N=2,113)	-5.71 (-9.75,-1.67)**	-4.25 (-6.62,-1.87)**	-1.46 (-3.34,0.43)	-0.03 (-0.07,0.02)	-0.03 (-0.08,0.02)
Glucose (N=2,114)	-1.91 (-5.97,2.15)	-1.36 (-3.75,1.03)	-0.54 (-2.43,1.35)	-0.04 (-0.09,0.01)	0.01 (-0.04,0.05)
Total Cholesterol (N=2,144)	-1.14 (-5.17,2.89)	-0.70 (-3.07,1.67)	-0.45 (-2.33,1.43)	0.02 (-0.02,0.07)	-0.03 (-0.07,0.02)
HDL Cholesterol (N=2,145)	3.80 (-0.22,7.81)	2.70 (0.34,5.06)*	1.08 (-0.79,2.96)	0.06 (0.01,0.11)*	-0.03 (-0.07,0.02)
Triglycerides (N=2,142)	-3.03 (-7.05,0.99)	-1.55 (-3.91,0.82)	-1.49 (-3.37,0.39)	-0.02 (-0.07,0.02)	-0.02 (-0.06,0.03)

Values are linear regression coefficients (95% confidence intervals) and reflect the change in cm³ of childhood brain global volumetric and in standard deviation scores of global white matter microstructure measures for maternal cardiovascular risk factors in standard deviation scores. Models are adjusted for child sex and age at the neuroimaging assessment. Systolic and diastolic blood pressure models are additionally adjusted for maternal height. *p < 0.05. ** p < 0.01.

Table S4. Maternal cardiovascular risk factors in early pregnancy and childhood global white matter microstructure measures at 10 years, follow-up analysis.

Maternal cardiovascular risk factors (SDS)	Global white matter microstructure measures (SDS)			
	Fractional Anisotropy	Mean Diffusivity	Radial Diffusivity	Axial Diffusivity
Systolic blood pressure (N= 2,777)	0.02 (-0.03,0.07)	-0.05 (-0.09,-0.00)*	-0.04 (-0.09,0.01)	-0.05 (-0.09,-0.00)*
Diastolic blood pressure (N=2,777)	0.01 (-0.04,0.06)	-0.07 (-0.11,-0.02)**	-0.05 (-0.09,-0.00)*	-0.08 (-0.12,-0.03)**

Values are linear regression coefficients (95% confidence intervals) and reflect the change in standard deviation scores of global white matter microstructure measures for maternal cardiovascular risk factors in standard deviation scores. Models are adjusted for child sex and age at the neuroimaging assessment and maternal height, age, ethnicity, educational level, parity, pregnancy-specific anxiety and smoking, alcohol and folic acid use during pregnancy. *p < 0.05. ** p < 0.01.

Figure S1. Flowchart of study population.

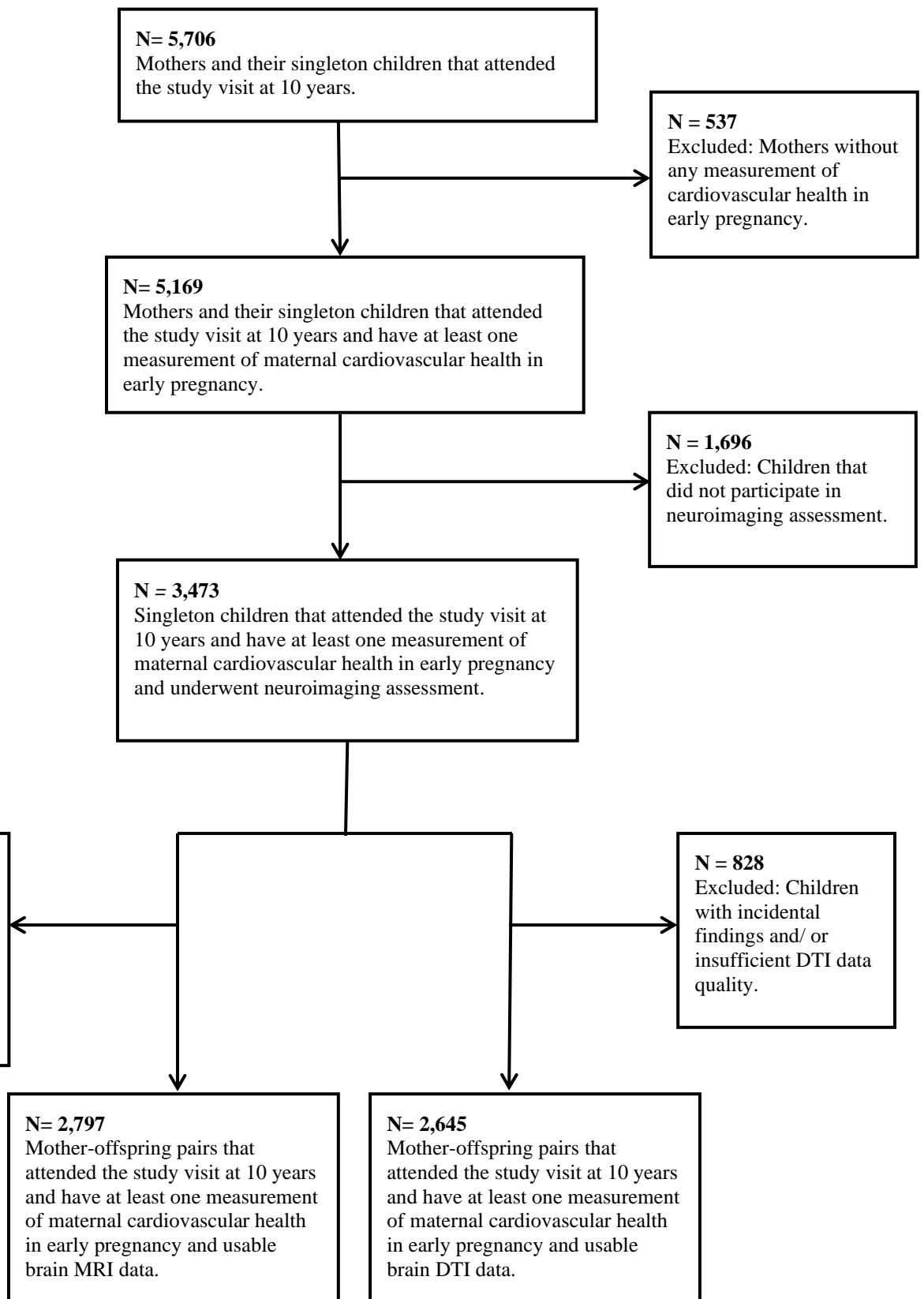


Figure S2. Simplified Directed Acyclic Graph showing the hypothesized relationship between maternal cardiovascular risk factors in early pregnancy and childhood brain structure and the covariates.

