Brain Volumes and Abnormalities in Adults Born Preterm at Very Low Birth Weight

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Objectives To assess radiographic brain abnormalities and investigate volumetric differences in adults born preterm at very low birth weight (<1500 g), using siblings as controls.

Study design We recruited 79 adult same-sex sibling pairs with one born preterm at very low birth weight and the sibling at term. We acquired 3-T brain magnetic resonance imaging from 78 preterm participants and 72 siblings. A neuroradiologist, masked to participants' prematurity status, reviewed the images for parenchymal and structural abnormalities, and FreeSurfer software 6.0 was used to conduct volumetric analyses. Data were analyzed by linear mixed models.

Results We found more structural abnormalities in very low birth weight participants than in siblings (37% vs 13%). The most common finding was periventricular leukomalacia, present in 15% of very low birth weight participants and in 3% of siblings. The very low birth weight group had smaller absolute brain volumes (−0.4 SD) and, after adjusting for estimated intracranial volume, less gray matter (−0.2 SD), larger ventricles (1.5 SD), smaller thalami (−0.6 SD), caudate nuclei (−0.4 SD), right hippocampus (−0.4 SD), and left pallidum (−0.3 SD). We saw no volume differences in total white matter (−0.04 SD; 95% CI, −0.13 to 0.09).

Conclusions Preterm very low birth weight adults had a higher prevalence of brain abnormalities than their term-born siblings. They also had smaller absolute brain volumes, less gray but not white matter, and smaller volumes in several gray matter structures. *(J Pediatr 2022;246:48-55)*.

Preterm delivery is a common adverse event affecting 10%-11% of all births worldwide, with 1%-2% of all infants born very preterm (<32 weeks) or at very low birth weight (<1500 g).[1] Many chronic diseases in adulthood are believed to originate during fetal life and childhood. For example, children and adults born preterm display more cardiovascular risk factors.[2-7] Very preterm/very low birth weight children and adults also display poorer executive functioning and a lower IQ by 12-13 points.[8-10] There seems to be a dose-effect relationship between birth weight and health outcomes: very preterm/very low birth weight individuals show more adverse health outcomes than participants born late preterm (34-36 completed weeks).[11]

Perinatally, very preterm/very low birth weight infants are susceptible to hemorrhage and sensitive to hypoxic events, which may in turn manifest as white matter (WM) injury in the preterm brain.[12-14] An important outcome of hypoxic-ischemic damage to the preterm brain is periventricular leukomalacia (PVL), potentially manifesting as motor impairment, cerebral palsy, or epilepsy.[15,16] A systematic review approximated the prevalence of PVL in very preterm/very low birth weight infants to be 7%-40%, with the prevalence being lower in ultrasound examination than in magnetic resonance (MR)-based studies, and inversely correlated with gestational age.[17,18] A greater proportion of abnormal brain MR scans have been reported in very preterm adolescents when compared with matched term controls (55% vs 5%).[19]

In addition to neuroradiographic signs of injury, brain manifestations in children and adults born very preterm/very low birth weight include smaller total brain volume and lesser amounts of both gray and WM.[20-23] The importance of WM abnormalities is emphasized by findings that children

BMI	Body mass index
GM	Gray matter
eTIV	Estimated total intracranial volume
PVL	Periventricular leukomalacia
WM	White matter

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born preterm without abnormalities in cerebral WM on a neonatal brain magnetic resonance imaging (MRI) seem to be largely spared from prematurity-associated cognitive problems in early childhood.[24,25]

Studies assessing the volumes of specific brain components in children and adults born very preterm/very low birth weight have consistently shown smaller volumes of basal ganglia, hippocampi, and cerebellum, which may be accompanied by larger ventricles of a characteristic morphology, in part owing to WM reduction.[22,26-29] The volumetric differences are more pronounced with an earlier gestational age and lower birth weight, are seen in early childhood, and may remain visible in later life.[24,30]

Previous studies of brain structure have focused on volumetry, contained small samples, and with one exception, used unrelated individuals born at term as controls.[23] Using a sibling control allows taking shared environmental and genetic confounders into account. Additionally, few studies have assessed how underlying conditions, such as preeclampsia or intrauterine growth restriction, contribute to brain findings in very low birth weight adults, which may be related to more severe sequelae than preterm birth alone. Our goal was to study pathological findings in adults born at very low birth weight from a neuroradiographic perspective and brain volumes in this unique setting using siblings as controls. We hypothesized that adults born at very low birth weight would have more incidental findings, smaller total brain volumes, as well as less gray matter (GM) and WM than their siblings. We also compared volumes of other specific brain structures.

Methods

Our recruitment process has been outlined in detail previously.[31] In brief, we recruited 79 adult same-sex sibling pairs, in which one sibling was born at very low birth weight and the other at term with a maximum age difference of 10 years. Suitable participants were identified from 3 geographically defined sources, based on residence or birth at a tertiary hospital serving a specific catchment area in Finland. They included 2 cohort studies: The Helsinki Study of Very Low Birth Weight Adults (Province of Uusimaa), and the Ester Preterm Birth Study (Provinces of Oulu and Lapland), and the Finnish Medical Birth Register corresponding to present-day provinces of Uusimaa, Southwest Finland, and Pirkanmaa.[3,5] All very low birth weight participants were born between 1978 and 1990. Exclusion criteria were pregnancy, endocrine disorders that might affect measurements, gross sensory or motor disorders (eg, cerebral palsy, blindness), ongoing oral steroid treatment, and not actually fulfilling the inclusion criteria (sibling turned out not to be term born based on hospital record review) (**Figure 1**; available at www.jpeds.com). After data collection, 4 siblings were excluded from the analyses owing to their birth records revealing a gestational age of less than 37 weeks. Two participants were excluded during the study owing to becoming pregnant after signing consent and one owing to a disability that was not apparent in the recruiting phase. Three term siblings withdrew before giving consent but their very low birth weight siblings still participated. A total of 150 suitable participants (78 very low birth weight and 72 term siblings) underwent brain MRI.

The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the study protocol and the participants signed informed consent. The study was conducted in accordance with the Declaration of Helsinki. All incidental findings were reported to the participants as stated in the study protocol and further medical attention was given when required.

The imaging was conducted as part of a comprehensive assessment with 3 clinical study visits occurring between June 2014 and June 2017. The participants underwent anthropometric measurements and completed questionnaires regarding family history, lifestyle, medications, and health during the clinical study visits.

We used a 3.0 T Magnetom Verio MR imager (Siemens) with a 32-channel head coil for brain imaging. We instructed the participants to abstain from eating and drinking for 4 hours beforehand and to avoid alcohol, sauna, and strenuous exercise for 2 days before imaging. The imaging took place during weekends at any time or weekdays between 8 AM and 12 PM. T1-weighted magnetization prepared rapid-gradient echo volumes were acquired using Siemens tfl3d1ns pulse sequence with flip angle of 9°, TR of 1900 ms, TI of 900 ms, and TE of 2.32 ms. There were 192 images in the sagittal plane with isotropic 0.9 × 0.9 × 0.9 mm^3 voxels that were obtained using a slice thickness of 0.9 mm, a field of view of 230 × 230 cm and acquisition matrix of 256 × 256. The imaging protocol further contained coronal T2-weighted turbo spin echo images (TR 4171 ms; TE 96 ms; slice thickness 4 mm), and axial T2-weighted fluid-attenuated inversion recovery images (TI 2500 ms; TR 9000 ms; TE 91 ms; slice thickness 4 mm). All 150 participants had sagittal T1-MPR, coronal T2-turbo spin echo and axial T2-fluid-attenuated inversion recovery or T2-turbo spin echo images collected.

A neuroradiologist with more than 10 years of experience, masked to the participants' prematurity status, reviewed the MR images. WM abnormalities were assessed with regard to volume loss, location, and cystic lesions. PVL was confirmed by 1 or both of 2 main findings: the presence of typical WM lesions or PVL-associated ventricular morphology (**Figure 2**; available at www.jpeds.com). Other abnormalities or pathologies were reported according to normal clinical standards.

Volumetric analyses were conducted using the T1-weighted magnetization prepared rapid-gradient echo images and the freely available FreeSurfer software suite (version 6.0) (http://surfer.nmr.mgh.harvard.edu/). The Freesurfer analysis software enables both fully automated segmentation workflow and semi-automatic workflow consisting of manual edits. The fully automated approach has been validated with manual segmentations, semiautomatic

workflow consisting of manual edits, and other software.[32-34] GM and WM volumes, cerebellum volume, total intracranial volume, total parenchyma volume, and the volumes of individual structures were obtained using the fully automated surface and volume-based processing pipelines of the Freesurfer software.[32,35] Brain volumes were measured in cubic millimeters and a quality control of the images was conducted before the FreeSurfer analysis. All images were inspected for errors in WM and GM delineation and subcortical segmentation using FreeSurfer software's Freeview tool. Eight very low birth weight participants and 4 term siblings had errors that were all related to ventricles being missegmented as WM hypointensity. These errors were corrected manually using FreeSurfer's guidelines with version 6.0.0 and inspected again to ensure data quality after rerunning the pipelines.

Statistical Analyses

All statistical analyses were conducted with IBM SPSS (version 27; IBM). Paired 2-tailed *t* tests were used for continuous variables and χ^2 test or Fisher exact test were used for nominal variables. A difference of *P* of less than .05 was considered statistically significant unless stated otherwise. We used linear mixed models to assess the effect of very low birth weight status on brain volumes with participants nested within families. We used the following variables as fixed effects: for model 1, we adjusted for age and sex; for model 2, we further adjusted for maternal age, maternal body mass index (BMI), maternal smoking during pregnancy, and primiparity; and for model 3, we adjusted further with estimated total intracranial volume (eTIV). Group differences in volumetric analyses were completed with whole volumes and adjusted for total intracranial volume instead of tissue volume to account for potential atrophy. Benjamini-Hochberg false discovery rate corrections were performed to correct for multiple testing regarding volumetric outcomes.

Data on maternal smoking were available for 95% (of all participants n = 142), and the variables were dummy coded for 2 variables (1 = smoking; 0 = nonsmoking or unknown, and conversely 1 = nonsmoking; 0 = smoking or unknown) for linear mixed model analyses. Maternal BMI was available for 97% of all participants (n = 146), and unknown data were imputed using linear regression of maternal BMI difference and maternal age difference between pregnancies from available cohort and sibling data. Gestational hypertension classes were defined as described previously.[36]

Results

As outlined earlier, 78 very low birth weight participants and 72 term siblings completed the brain MRI successfully. By design, mean age at clinical visit showed higher variability in the sibling controls (SD of 2.6 years in very low birth weight participants, 4.9 years in controls), but the mean itself was similar (29.4 years in the very low birth weight group, 29.1 years in the sibling group). The very low birth weight participants were shorter and very low birth weight men weighed less than the sibling group, but the groups were similar regarding BMI (**Table I**).

The very low birth weight group displayed more PVL and PVL-like lesions than their term siblings: 15.4% vs 2.8%. The very low birth weight participants also displayed more other individual lesions and variants, but too few of each to allow separate statistical comparison. When grouped together, the very low birth weight group had a larger number of any findings than the sibling group: 37.2% vs 12.5%. Noteworthy lesions and variants, many limited to the very low birth weight group, included nonspecific WM lesions, pineal cysts, arachnoid cysts, and cavum septum pellucidum (**Table II**).

To calculate the mean differences in brain volumes, we used linear mixed models with maximum likelihood and present estimates from model 3 in **Table III** and **Table IV**. The volumes described in this paragraph are, unless otherwise pointed out, from model 3, which adjusts for sex, age, maternal smoking, maternal BMI, maternal age, primiparity, and eTIV. Results from all models are presented separately (**Tables V** and **VI**; available at www.jpeds.com).

The linear mixed models showed a difference in total brain volume in all models: a difference of −13 240 mm^3 (−0.10 SD; 95% CI, −24 570 to −1900). The total GM volume was smaller in very low birth weight participants than their term siblings with a difference of −10 950 mm^3 (−0.16 SD; 95% CI, −18 420 to −3490), with cortical GM being less affected than deep GM, −6520 mm^3 and –2010 mm^3, respectively (−0.12 SD and −0.35 SD; 95% CI, −13 110 to 70 and –2780 to −1240). In both whole and cerebral WM, no difference could be seen, −2510 mm^3 and –1490 mm^3, respectively (−0.04 SD and −0.02 SD; 95% CI, −9890 to 4880 and 95% CI, −8510 to 5530). Cerebellar volumes were smaller in very low birth weight participants with a difference of −3660 mm^3 (−0.21 SD; 95% CI, −6670 to −640). Total ventricular volume was larger in the very low birth weight group, 10 030 mm^3 (+1.45 SD; 95% CI, 5880 to 14 180). We then conducted correction for multiple testing by the Benjamini-Hochberg method (**Tables V** and **VI**). All differences remained statistically significant with the exception of the left putamen, for which significance level was 0.09 (without correction 0.05).

At a more refined structural volumetric level, the linear mixed model showed very low birth weight individuals having smaller thalami (right −0.63, left −0.50 SD), caudate nuclei (right −0.39, left −0.40 SD), left putamen (−0.22 SD), left pallidum (−0.26 SD), and right hippocampus (−0.35 SD). The amygdalae or nuclei accumbens, in contrast, showed no difference in volumes (**Table IV**).

We performed secondary analyses to investigate the relationship between small for gestational age status and brain volumes, and pre-eclampsia and brain volumes in very low birth weight participants using linear mixed models with term siblings as the reference category (**Table VII** and **Table VIII**; available at www.jpeds.com). The small for gestational age-very low birth weight group showed less total brain volume (−0.72 SD vs −0.24 SD) and less GM

Table I. Demographic and anthropometric characteristics of very low birth weight participants and their term siblings (n = 150; 53% women)

Characteristics	Very low birth weight group (n = 78)		Sibling group (n = 72)		*P* value
	Mean/n (%)	SD (min-max)	Mean/n (%)	SD (min-max)	
Neonatal characteristics					
Gestational age (wk)	29.6	2.5 (23.9-36.4)	39.8	1.3 (37.0-42.1)	<.001
Birth weight (g)	1150	221 (640-1500)	3390	431 (2100-4470)	<.001
Small for gestational age	29 (37.2%)		2 (2.8%)		<.001
Primiparous	29 (37.2%)		24 (33.3%)		.62
Family characteristics					
Highest parental education*					
Lower secondary or lower			0%		
Higher secondary			38.6%		
Tertiary			61.4%		
Maternal age at birth (y)	29.7	4.9	30.1	5.0	.57
Maternal BMI (kg/m^2) (n = 146)	22.5	4.2	22.6	4.2	.86
Gestational hypertension					
Nonhypertensive	50 (64.1%)		47 (65.3%)		.88
Gestational and chronic hypertension	4 (5.1%)		18 (25.0%)		.001
Pre-eclampsia and superimposed pre-eclampsia	21 (26.9%)		1 (1.4%)		<.001
Only proteinuria	3 (3.8%)		6 (8.3%)		.25
Maternal smoking during pregnancy (n = 142)	11 (14.1%)		11 (15.3%)		.72
Participant characteristics					
Age (y)	29.4	2.6	29.1	4.9	.72
Height women (cm)	162.3	7.1	165.7	5.5	.021
Height men (cm)	174.0	7.8	180.0	6.9	.001
Weight women (kg)	63.4	15.4	65.3	15.1	.57
Weight men (kg)	75.4	12.8	83.6	14.6	.015
BMI (kg/m^2) women	24.0	5.4	23.7	5.0	.81
BMI (kg/m^2) men	24.9	3.9	25.7	3.9	.37

Small for gestational age is < −2 SD.
*The highest parental education is shared by siblings and is identical within families.

(−0.71 SD vs −0.31 SD) and total WM (−0.68 SD vs −0.15 SD) than the appropriate for gestational age group when compared with term siblings in model 1 and were of a similar magnitude in model 2. The differences attenuated in model 3 when adjusting for eTIV. Compared with the sibling group, the pre-eclampsia-very low birth weight

Table II. MR findings in very low birth weight participants and their term siblings

Findings	Very low birth weight (n, %)	Sibling (n, %)	*P* value
PVL-related findings			
PVL or PVL-like findings*	12 (15.4%)	2 (2.8%)	.01
Porencephalic cyst*	4 (5.1%)	0	.12
Other findings			
Unspecific WM lesion*	6 (7.7%)	3 (4.2%)	.50
Chiari 1*	2 (2.5%)	0	.50
Postintracranial hemorrhage, status*	0	1 (1.4%)	.48
Atrophy of cerebellum*	1 (1.3%)	0	>.99
Polymicrogyria*	1 (1.3%)	0	>.99
Pineal cyst*	2 (2.8%)	2 (2.8%)	>.99
Spinal cyst*	1 (1.3%)	0	>.99
Septo-optic dysplasia*	1 (1.3%)	0	>.99
WM reduction*	1 (1.3%)	0	>.99
Posthydrocephalic status*	1 (1.3%)	0	>.99
Arachnoid cyst*	3 (3.8%)	2 (2.8%)	>.99
Agenesis of corpus callosum*	1 (1.3%)	0	>.99
Developmental venous anomaly*	1 (1.3%)	0	>.99
Cavum velum interpositum cyst*	1 (1.3%)	0	>.99
Unspecific gliosis*	1 (1.3%)	0	>.99
Glioma suspicion*	0	1 (1.4%)	.48
Septum pellucidum*	1 (1.3%)	1 (1.4%)	>.99
Any finding†	29 (37.2%)	9 (12.5%)	<.001

*Fisher exact test.
†χ^2 test.

Table III. Fixed effect estimates (SD units, 95% CIs) in volumes (mm^3) of brain between very low birth weight adults and sibling-controls born at term, adjusted for covariates

Brain structure	Mean for sibling controls	Mean difference		SD units	95% CI lower limit	95 % CI upper limit
Total brain volume (mm^3)	1 220 640	−13 240	*	−0.10	−24 570	−1900
Total GM (mm^3)	705 510	−10 950	*	−0.16	−18 420	−3490
Cerebral cortical GM (mm^3)	520 750	−6520		−0.12	−13 110	70
Subcortical GM (mm^3)	59 900	−2010	*	−0.35	−2780	−1240
Total WM (mm^3)	515 430	−2510		−0.04	−9890	4880
Cerebral WM (mm^3)	482 210	−1490		−0.02	−8510	5530
Ventricles (mm^3)	19 010	10 030	*	1.45	5880	14 180

Linear mixed models adjusted for sex, age, maternal smoking during pregnancy, maternal BMI, maternal age, primiparity, and eTIV.
*$P < .05$.

group's volumes were smaller than the non-pre-eclampsia-very low birth weight group's in the same areas as in the small for gestational age-very low birth weight groups, but the results did not reach significance for total brain volume (−0.67 SD vs −0.32 SD; $P = .07$), GM (− 0.65 SD vs −0.38 SD; $P = .10$) or total WM (−0.64 SD vs −0.23 SD; $P = .06$), and attenuated when adjusting for eTIV in model 3.

Discussion

We investigated adult brain volumes of very low birth weight infants and their siblings born at term. We also examined whether very low birth weight individuals have neuroradiographic findings as potential adult sequelae of preterm birth. Very low birth weight adults had more brain abnormalities and variations as well as smaller brain volumes. These differences were present when compared with sibling controls, and thus, are not likely owing to unmeasured confounders shared by siblings.

It is well-known that radiological examinations yield a high number of incidental findings of varying clinical significance, with brain MRI being no exception. Few studies report the prevalence of radiological findings, whereas we pursued identification of neuroradiographic adult very low birth weight outcomes with potential clinical significance. We found that very low birth weight individuals show more incidental findings in the brain than their term siblings, some reflecting pathology and some harmless variants, with PVL being the most prevalent finding. An umbrella review found that incidental findings are present in 22% of all brain MRIs (95% CI, 14%-31%).[37] Our findings of very low birth weight individuals having more incidental findings (37% vs 13%) than term siblings is noteworthy and is supported by a study of very preterm adolescents and young adults.[19,29] The number of incidental findings in siblings is in line with the general population. The high prevalence of structural brain abnormalities suggests that prematurity could be linked to some etiology from early life, and preterm birth in itself is not always responsible for brain abnormalities found in MRI.

Previous research on very low birth weight has consistently shown lesser total brain volumes, but the results regarding volume loss in GM and WM have shown heterogeneity, possibly owing to methodological differences, residual confounding elements, or insufficient power, which are factors

Table IV. Fixed effect estimates (SD units, 95% CIs) in volumes (mm^3) of different brain structures between very low birth weight adults and sibling-controls born at term, adjusted for covariates

Brain structure	Mean for sibling controls	Mean difference		SD units	95% CI lower limit	95 % CI upper limit
Right thalamus (mm^3)	7820	−550	*	−0.63	−720	−380
Left thalamus (mm^3)	8090	−430	*	−0.50	−600	−260
Right caudate nucleus (mm^3)	3490	−160	*	−0.39	−240	−70
Left caudate nucleus (mm^3)	3460	−160	*	−0.40	−250	−60
Right putamen (mm^3)	5090	−90		−0.16	−190	20
Left putamen (mm^3)	4960	−120	*	−0.22	−240	0
Right pallidum (mm^3)	1950	0		−0.01	−50	40
Left pallidum (mm^3)	2050	−70	*	−0.26	−110	−20
Right hippocampus (mm^3)	4440	−170	*	−0.35	−250	−90
Left hippocampus (mm^3)	4250	−70		−0.14	−160	20
Right amygdala (mm^3)	1870	30		0.10	−20	70
Left amygdala (mm^3)	1730	10		0.04	−40	60
Right nucleus accumbens (mm^3)	550	0		0.02	−20	20
Left nucleus accumbens (mm^3)	460	−10		−0.18	−40	10

Linear mixed models adjusted for sex, age, maternal smoking during pregnancy, maternal BMI, maternal age, primiparity, and eTIV.
*$P < .05$.

that our study addresses. The findings of lesser total brain and GM volumes were largely corroborated in our sibling comparisons, suggesting they are not explained by differences in genetic makeup or environmental exposures. Contrary to many previous reports with younger participants, we did not observe a difference in WM volume. A follow-up study with a sample closer to our participants' age group, however, saw no difference in WM volume, which was suggested to be attributable to brain maturation in the very low birth weight group.[21,38]

Fearon et al had term siblings as controls for very low birth weight participants (mean age, 23 years; 18 siblings; 33 very low birth weight participants) and reported 4.8 mL larger ventricles in the very low birth weight group, but could not detect statistically significant differences in cerebral GM, with a difference in mean volumes of 34 mL, or hippocampi.[23] The volumes of basal ganglia or WM were not reported. The magnitude of mean differences was, however, similar to model 1 in our results. That these differences reached statistical significance in our study, but not in the Fearon et al study, may be due to less power in the latter.

The third trimester is crucial for brain development, particularly GM. Munakata et al have studied 16 preterm infants with 13 term infants and compared their brain volumes at term-equivalent age against lipidomics.[39] They suggest that nutrition, particularly fat intake, plays an important role in brain maturation and GM development in preterm infants.[39,40] Based on this finding, we can speculate that the lesser GM volumes seen in our study could be due to interrupted development or suboptimal nutritional postpartum environment. the decrease in total GM volume ($-10\ 950\ mm^3$) and increase in ventricle size ($10\ 030\ mm^3$) in our study are of a similar magnitude, suggesting a role for GM decrease as well. The increased ventricular volume in individuals born preterm has mostly been attributed to smaller volumes of WM.[41] We expect further clarity regarding the relationship between parenchymal and ventricular volumes could be attained by potential future longitudinal volumetric studies.

A meta-analysis of very low birth weight children and adolescents reported a decrease in WM of −0.53 SD (95% CI, −0.4 to −0.62 SD), whereas in our study the mean difference of WM volume was $-2510\ mm^3$ (−0.04 SD; 95% CI, −0.13 to 0.09 SD), implying no difference.[22] Our finding of no difference may be due to our design that allows adjusting for a larger number of genetic and environmental confounding factors than previous studies. It has been shown in numerous works that there is a high degree of heritability in total brain volume as well as GM and WM volumes.[42-44] A part of the volumetric differences observed by others might thus be hereditary, and the similarity in WM volume may also be attributable to confounding factors our design can address. As a counterhypothesis, the similarity may be unrelated to the sibling setting and owing to normal brain maturation. It is known that the ratio of WM to GM tends to increase with growth, a phenomenon seen both in term and very low birth weight individuals in adulthood.[21] In contrast, the differences in WM between very low birth weight and term individuals are still seen in children and teenagers, but the difference diminishes with age.[21] This could explain the lack of difference in WM volumes in our sibling setting in our participants in their 30s, when adjusting for eTIV. When not adjusting for eTIV, but including all other covariates (as done in model 2, **Table V**), we see a significant −0.35 SD difference in WM volume between groups. This would imply that unadjusted observed adult differences in WM volumes could mostly be attributed to head size, which should be taken into account in future studies.

With the exception of WM, the majority of previously reported findings regarding smaller brain volumes and larger ventricles were replicated by our sibling design. Volumetric differences between very low birth weight participants and their term siblings could be due to maturation differences or insults not visible on imaging. The mechanism behind this difference could be hypoxic or metabolic in nature affecting either the development of the aforementioned structures, or the differences could present a result of parenchymal damage. The observed differences in volumes of several structures' significance attenuated when adjusting for eTIV, meaning that the smaller size of these structures was in part, but not exclusively, owing to smaller intracranial volume.

Although being born small for gestational age or having pre-eclampsia are major comorbidities of very low birth weight birth, their effect on structural brain alterations in adults has not been well studied. The supplementary analyses regarding small for gestational age and pre-eclampsia suggest that these subgroups could have even more pronounced volumetric differences than just being born at very low birth weight alone. Being born at small for gestational age and pre-eclampsia, as well as being very low birth weight, could thus pose an even higher risk of developing health issues related to prematurity, but this merits further research; the number of individuals with a history of small for gestational age or pre-eclampsia is fairly low in our study.

A possible limitation to our study is inherent in its design. In studying siblings, we can eliminate much of confounding by genetic background and environmental factors, shared within family. Differences between siblings constitute therefore a relatively strong argument towards causality. However, when differences between very low birth weight and the general population are of interest, sibling-design does have limitations. Because the first contact with the term sibling was made through the very low birth weight sibling, it is possible that siblings close to each other may have been more likely to participate. Such siblings could also be more similar in lifestyle and health, which would be expected to produce more conservative estimates.

Because our study excluded individuals with cerebral palsy and major sensorimotor disabilities, we expected the most severe forms of brain differences to be absent from our population. Our findings in the non-affected participants may thus represent a conservative estimation of the whole very low birth weight adult population. The groups nonetheless

showed marked differences, especially in the prevalence of PVL and PVL-like lesions. Arguably, the developing brain might be so resilient that although young very low birth weight adults display imaging findings of brain damage, the actual manifestations remain subclinical or entirely absent. ■

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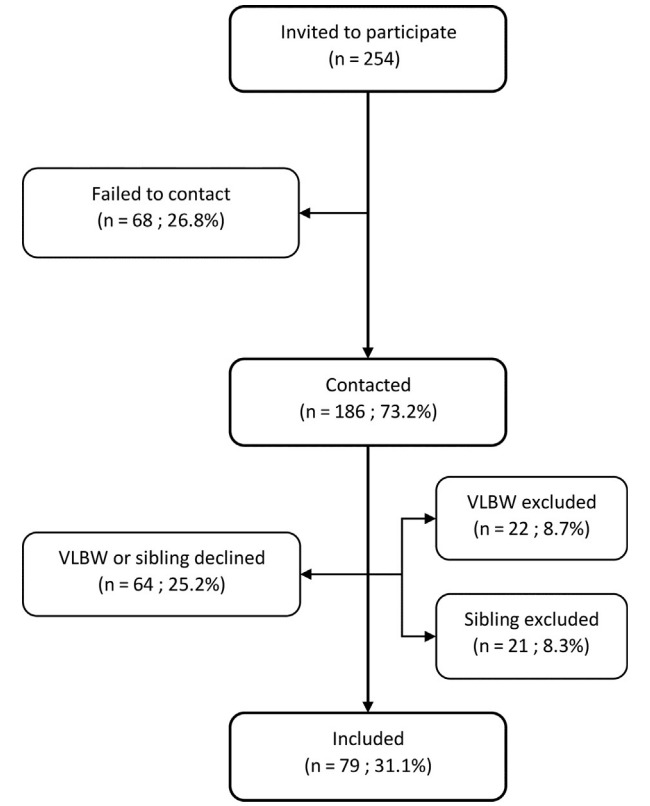

Figure 1. Flowchart of the recruitment process. n = sibling pair.

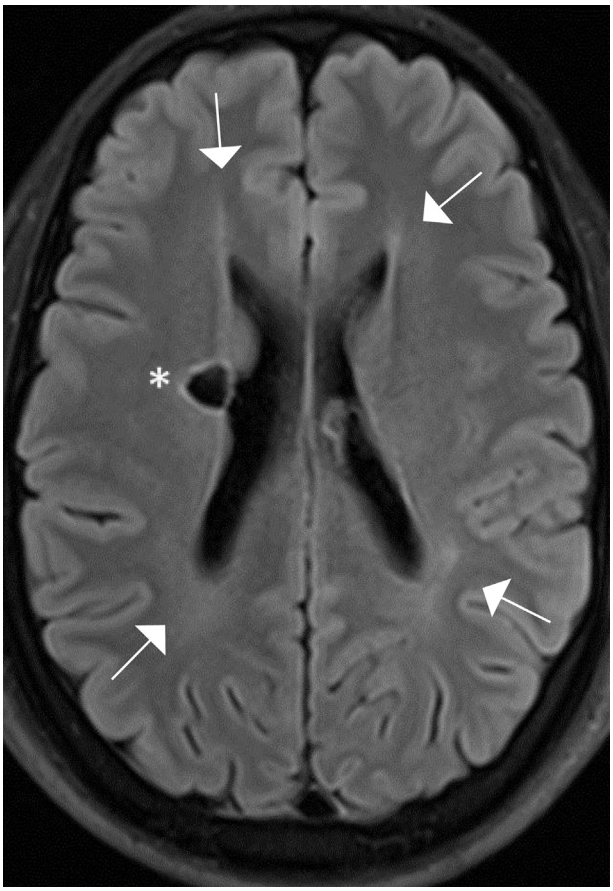

Figure 2. A T2-fluid-attenuated inversion recovery image showing typical patchy PVL WM lesions around the ventricular horns (*arrows*) and a periventricular porencephalic cyst (*asterisk*) on the right, consistent with PVL. There is minor retraction around the ventricular horns with slight sharpening anteriorly and a rounded configuration posteriorly peritrigonally.

Table V. Fixed effect estimates (SD units, 95% CIs) in volumes (mm^3) of brain and individual structures between very low birth weight adults and sibling controls born at term, adjusted for covariates

Brain structure	Mean for sibling controls	Mean difference		SD units	95% CI lower limit	95 % CI upper limit	Unadjusted *P* values	BH-corrected *P* values
Total brain volume (mm^3)	1 220 640							
Model 1		−53 800	*	−0.41	−79 410	−28 200	<.01	<.01
Model 2		−55 900	*	−0.43	−81 200	−30 610	<.01	<.01
Model 3		−13 240	*	−0.10	−24 570	−1900	<.01	<.01
Total GM (mm^3)	705 510							
Model 1		−31 600	*	−0.45	−45 110	−18 100	<.01	<.01
Model 2		−32 710	*	−0.47	−46 180	−19 230	<.01	<.01
Model 3		−10 950	*	−0.16	−18 420	−3490	<.01	.01
Cerebral cortical GM (mm^3)	520 750							
Model 1		−22 260	*	−0.41	−33 320	−11 200	<.01	<.01
Model 2		−23 130	*	−0.42	−34 170	−12 100	<.01	<.01
Model 3		−6520		−0.12	−13 110	70	.05	.09
Subcortical GM (mm^3)	59 900							
Model 1		−3610	*	−0.64	−4820	−2410	<.01	<.01
Model 2		−3660	*	−0.65	−4850	−2470	<.01	<.01
Model 3		−2010	*	−0.35	−2780	−1240	<.01	<.01
Total WM (mm^3)	51 5430							
Model 1		−22 680	*	−0.34	−36 390	−8970	<.01	<.01
Model 2		−23 700	*	−0.35	−37 170	−10 220	<.01	<.01
Model 3		−2510		−0.04	−9890	4880	.50	.61
Cerebral WM (mm^3)	482 210							
Model 1		−21 000	*	−0.33	−34 200	−7790	<.01	<.01
Model 2		−21 880	*	−0.34	−34 880	−8880	<.01	<.01
Model 3		−1490		−0.02	−8510	5530	.67	.76
Cerebellum (mm^3)	156 430							
Model 1		−7440	*	−0.42	−10 800	−4070	<.01	<.01
Model 2		−7630	*	−0.44	−10 990	−4270	<.01	<.01
Model 3		−3660	*	−0.21	−6670	−640	.02	.04
Ventricles (mm^3)	19 010							
Model 1		8770	*	1.27	4810	12 740	<.01	<.01
Model 2		8860	*	1.28	4840	12 880	<.01	<.01
Model 3		10 030	*	1.45	5880	14 180	<.01	<.01

P values are displayed as unadjusted and after Benjamini-Hochberg false discovery rate correction.
Model 1 is adjusted for sex and age.
Model 2 is further adjusted for maternal smoking during pregnancy, maternal BMI, maternal age, and primiparity.
Model 3 is further adjusted for eTIV.
*$P < .05$.

Table VI. Fixed effect estimates (SD units, 95% CIs) in volumes (mm^3) of different brain structures between very low birth weight adults and sibling-controls born at term, adjusted for covariates

Brain structure	Mean for sibling controls	Mean difference		SD units	95% CI lower limit	95 % CI upper limit	Unadjusted *P* values	BH-corrected *P* values
Right thalamus (mm^3)	7820							
Model 1		−760	*	−0.87	−980	−540	<.01	<.01
Model 2		−780	*	−0.89	−1000	−560	<.01	<.01
Model 3		−550	*	−0.63	−720	−380	<.01	<.01
Left thalamus (mm^3)	8090							
Model 1		−630	*	−0.74	−850	−420	<.01	<.01
Model 2		−640	*	−0.75	−850	−430	<.01	<.01
Model 3		−430	*	−0.50	−600	−260	<.01	<.01
Right caudate nucleus (mm^3)	3490							
Model 1		−270	*	−0.67	−370	−160	<.01	<.01
Model 2		−260	*	−0.66	−370	−160	<.01	<.01
Model 3		−160	*	−0.39	−240	−70	<.01	<.01
Left caudate nucleus (mm^3)	3460							
Model 1		−260	*	−0.67	−370	−150	<.01	<.01
Model 2		−260	*	−0.66	−360	−150	<.01	<.01
Model 3		−160	*	−0.40	−250	−60	<.01	.01
Right putamen (mm^3)	5090							
Model 1		−240	*	−0.43	−370	−110	<.01	<.01
Model 2		−240	*	−0.43	−370	−100	<.01	<.01
Model 3		−90		−0.16	−190	20	.09	.15
Left putamen (mm^3)	4960							
Model 1		−250	*	−0.45	−390	−120	<.01	<.01
Model 2		−250	*	−0.45	−390	−110	<.01	<.01
Model 3		−120	*	−0.22	−240	0	.05	.09
Right pallidum (mm^3)	1950							
Model 1		−60	*	−0.26	−120	0	.05	.06
Model 2		−60	*	−0.28	−120	0	.04	.05
Model 3		0		−0.01	−50	40	.95	.95
Left pallidum (mm^3)	2050							
Model 1		−120	*	−0.50	−180	−70	<.01	<.01
Model 2		−130	*	−0.53	−190	−80	<.01	<.01
Model 3		−70	*	−0.26	−110	−20	<.01	<.01
Right hippocampus (mm^3)	4440							
Model 1		−280	*	−0.58	−380	−190	<.01	<.01
Model 2		−280	*	−0.58	−380	−190	<.01	<.01
Model 3		−170	*	−0.35	−250	−90	<.01	<.01
Left hippocampus (mm^3)	4250							
Model 1		−170	*	−0.35	−270	−70	<.01	<.01
Model 2		−180	*	−0.36	−280	−80	<.01	<.01
Model 3		−70		−0.14	−160	20	.14	.20
Right amygdala (mm^3)	1870							
Model 1		−30		−0.11	−80	20	.22	.22
Model 2		−30		−0.10	−70	20	.28	.28
Model 3		30		0.10	−20	70	.25	.32
Left amygdala (mm^3)	1730							
Model 1		−40		−0.16	−100	10	.10	.11
Model 2		−40		−0.16	−90	10	.10	.11
Model 3		10		0.04	−40	60	.69	.76
Right nucleus accumbens (mm^3)	550							
Model 1		−20		−0.24	−40	0	.10	.11
Model 2		−20		−0.19	−40	10	.19	.20
Model 3		0		0.02	−20	20	.88	.92
Left nucleus accumbens (mm^3)	460							
Model 1		−30	*	−0.39	−50	−10	.01	.01
Model 2		−30	*	−0.35	−50	−10	.02	.02
Model 3		−10		−0.18	−40	10	.21	.29

P values are displayed as unadjusted and after Benjamini-Hochberg false discovery rate correction.
Model 1 is adjusted for sex and age.
Model 2 is further adjusted for maternal smoking during pregnancy, maternal BMI, maternal age, and primiparity.
Model 3 is further adjusted for eTIV.
*$P < .05$ before Benjamini-Hochberg false discovery rate correction.

Table VII. Exploratory analyses of the relationship between being born at very low birth weight and small for gestational age (<–2 SD) or appropriate for gestational age with term siblings as controls using linear mixed models

Models and covariates			Small for gestational age-very low birth weight-estimate	SE	SD units	Appropriate for gestational age-very low birth weight-estimate	SE	SD units	*P* value
Model 1	Total brain	*	−94 290	−18 240	−0.72	−31 370	14 410	−0.24	.003
Sex	Total GM	*	−49 380	9720	−0.71	−21 710	7710	−0.31	.01
Age	Cerebral cortical GM	*	−38 440	7890	−0.70	−13 190	6290	−0.24	.003
	Subcortical GM	†	−4870	860	−0.86	−2920	680	−0.52	.09
	Total WM	*	−45 380	9730	−0.68	−10050	7660	−0.15	.003
	Cerebral WM	*	−44 100	9320	−0.69	−8130	7340	−0.13	.002
	Cerebellum		−7400	2570	−0.42	−7460	2000	−0.43	.88
	Ventricles		9740	2780	1.41	8220	2280	1.19	.65
	Right thalamus	*	−980	150	−1.12	−640	130	−0.72	.04
	Left thalamus		−730	150	−0.85	−640	130	−0.67	.29
	Right caudate nucleus	*	−410	80	−1.02	−190	60	−0.47	.05
	Left caudate nucleus		−390	80	−0.99	−190	60	−0.49	.11
	Right putamen	†	−410	100	−0.75	−140	80	−0.26	.08
	Left putamen		−400	100	−0.71	−170	80	−0.30	.19
	Right pallidum	†	−130	40	−0.57	−20	30	−0.10	.05
	Left pallidum	†	−190	40	−0.75	−90	30	−0.36	.05
	Right hippocampus		−310	70	−0.64	−270	60	−0.54	.55
	Left hippocampus		−170	70	−0.35	−170	60	−0.34	.74
	Right amygdala		−50	40	−0.18	−20	30	−0.08	.59
	Left amygdala		−40	40	−0.16	−50	30	−0.17	.99
	Right nucleus accumbens	*	540	20	−0.60	0	10	−0.04	.04
	Left nucleus accumbens	*	−60	20	−0.78	−10	10	−0.17	.01
Model 2	Total brain	*	−101 050	18 110	−0.77	−32 260	13 990	−0.25	.001
Sex	Total GM	*	−52 590	9760	−0.75	−22 270	7580	−0.32	.01
Age	Cerebral cortical GM	*	−41 050	7900	−0.75		6160	−0.25	.002
Maternal smoking	Subcortical GM	*	−5080	850	−0.90	−2910	670	−0.51	.04
during pregnancy	Total WM	*	−48 890	9590	−0.73	−10 430	7400	−0.16	<.001
Maternal BMI	Cerebral WM	*	−47 380	9190	−0.74	−8420	7100	−0.13	<.001
Maternal age	Cerebellum		−7700	2600	−0.44	−7590	1980	−0.43	.74
First-born status	Ventricles		10 000	2830	1.45	8240	2290	1.19	.43
	Right thalamus	*	−1040	150	−1.18	−640	120	−0.73	.01
	Left thalamus		−760	150	−0.89	−580	120	−0.68	.19
	Right caudate nucleus	*	−410	80	−1.03	−190	60	−0.47	.02
	Left caudate nucleus	†	−380	80	−0.98	−190	60	−0.49	.08
	Right putamen	*	−430	100	−0.78	−140	70	−0.25	.04
	Left putamen		−410	100	−0.73	−170	80	−0.29	.14
	Right pallidum	*	−140	40	−0.61	−20	30	−0.11	.03
	Left pallidum	*	−200	40	−0.83	−90	30	−0.37	.02
	Right hippocampus		−320	70	−0.66	−260	60	−0.54	.47
	Left hippocampus		−190	70	−0.39	−170	60	−0.34	.55
	Right amygdala		−40	40	−0.17	−20	30	−0.07	.72
	Left amygdala		−50	40	−0.17	−40	30	−0.16	.98
	Right nucleus accumbens	†	−40	20	−0.51	0	10	−0.02	.05
	Left nucleus accumbens	*	−60	20	−0.74	−10	10	−0.15	.02
Model 3	Total brain		−21 380	8470	−0.16	−9590	6320	−0.07	.318
Sex	Total GM		−12 270	5490	−0.18	−10 340	4180	−0.15	.757
Age	Cerebral cortical GM		−10 400	4930	−0.19	−4770	3690	−0.09	.347
Maternal smoking	Subcortical GM		−1920	580	−0.34	−2050	430	−0.36	.847
during pregnancy	Total WM		−9710	5610	−0.14	670	4100	0.01	.170
Maternal BMI	Cerebral WM		−9980	5330	−0.16	2240	3880	0.04	.103
Maternal age	Cerebellum	†	230	2310	0.01	−5340	1670	−0.30	.097
First–born status	Ventricles		12 440	2960	1.80	8900	2310	1.29	.268
Estimated intracranial	Right thalamus		−610	120	−0.69	−520	90	−0.59	.296
volume	Left thalamus		−360	120	−0.42	−470	90	−0.54	.573
	Right caudate nucleus		−210	70	−0.53	−130	50	−0.33	.427
	Left caudate nucleus		−190	70	−0.50	−140	50	−0.36	.716
	Right putamen		−160	80	−0.29	−60	60	−0.10	.784
	Left putamen		−170	90	−0.30	−100	70	−0.18	.749
	Right pallidum		−30	30	−0.13	10	20	0.05	.564
	Left pallidum		−80	30	−0.34	−60	20	−0.23	.575
	Right hippocampus		−100	60	−0.20	−200	50	−0.41	.329
	Left hippocampus		20	70	0.03	−110	50	−0.22	.287
	Right amygdala		60	30	0.24	10	30	0.04	.138

(*continued*)

Table VII. Continued

Models and covariates		Small for gestational age-very low birth weight-estimate	SE	SD units	Appropriate for gestational age-very low birth weight-estimate	SE	SD units	*P* value
	Left amygdala	60	40	0.22	−10	30	−0.05	.124
	Right nucleus accumbens	−10	20	−0.13	10	10	0.09	.399
	Left nucleus accumbens	−30	20	−0.44	0	10	−0.06	.192

Fixed effects estimates (mm^3) with standard errors, SD units, adjusted for covariates. A statistical significance between the small for gestational age-very low birth weight and appropriate for gestational age -very low birth weight groups.

*$P < .05$.

†$P < .10$.

Table VIII. Exploratory analyses of the relationship between being born at very low birth weight with pre-eclampsia or superimposed pre-eclampsia with term siblings as controls using linear mixed models

Models and covariates			Very low birth weight + pre-eclampsia	SE	SD units	Very low birth weight, no pre-eclampsia	SE	SD units	*P* value
Model 1	Total brain	*	−87 510	20 980	−0.67	−41 500	13 950	−0.32	.07
Sex	Total GM	*	−45 060	11 150	−0.65	−26 670	7460	−0.38	.10
Age	Cerebral cortical GM	*	−34 970	9070	−0.64	−17 580	6100	−0.32	.05
	Subcortical GM		−4870	970	−0.86	−3160	650	−0.56	.25
	Total WM	*	−43 120	11 150	−0.64	−15 150	7390	−0.23	.06
	Cerebral WM	†	−42 140	10 700	−0.66	−13 190	7090	−0.21	.04
	Cerebellum		−6380	2920	−0.36	−7820	1900	−0.45	.51
	Ventricles		8900	3130	1.29	8730	2180	1.26	.97
	Right thalamus		−970	170	−1.11	−680	120	−0.78	.21
	Left thalamus		−710	170	−0.83	−600	120	−0.70	.72
	Right caudate nucleus	†	−480	80	−1.20	−190	60	−0.47	.01
	Left caudate nucleus	*	−440	90	−1.13	−200	60	−0.50	.08
	Right putamen		−380	110	−0.69	−190	70	−0.34	.20
	Left putamen		−360	110	−0.64	−210	80	−0.38	.38
	Right pallidum		−100	50	−0.47	−40	30	−0.19	.55
	Left pallidum		−170	50	−0.70	−110	30	−0.43	.42
	Right hippocampus		−370	80	−0.76	−250	50	−0.51	.28
	Left hippocampus		−230	80	−0.47	−150	60	−0.30	.62
	Right amygdala		−50	40	−0.20	−20	30	−0.08	.61
	Left amygdala		−10	40	−0.04	−60	30	−0.21	.47
	Right nucleus accumbens	*	−50	20	−0.62	−10	10	−0.10	.05
	Left nucleus accumbens		−50	20	−0.57	−30	10	−0.32	.27
Model 2	Total brain	†	−94 940	21 120	−0.73	−42 090	13 740	−0.32	.04
Sex	Total GM	*	−49 090	11 340	−0.70	−26 900	7430	−0.39	.07
Age	Cerebral cortical GM	†	−38 820	9210	−0.71	−17 560	6060	−0.32	.03
Maternal smoking during pregnancy	Subcortical GM		−5140	980	−0.91	−3140	640	−0.55	.19
	Total WM	†	−46 430	11 150	−0.69	−15 580	7240	−0.23	.04
Maternal BMI	Cerebral WM	†	−45 360	10 710	−0.71	−13 490	6960	−0.21	.02
Maternal age	Cerebellum		−6160	2970	−0.35	−8160	1900	−0.47	.43
First–born status	Ventricles		8880	3230	1.29	8860	2210	1.28	.97
	Right thalamus		−1040	170	−1.19	−690	120	−0.78	.16
	Left thalamus		−720	170	−0.84	−620	120	−0.72	.69
	Right caudate nucleus	†	−470	90	−1.19	−190	60	−0.48	.01
	Left caudate nucleus		−430	90	−1.10	−200	60	−0.51	.12
	Right putamen		−390	110	−0.72	−180	70	−0.33	.14
	Left putamen		−390	110	−0.70	−200	80	−0.36	.30
	Right pallidum		−120	50	−0.54	−40	30	−0.19	.26
	Left pallidum		−190	50	−0.78	−110	30	−0.44	.18
	Right hippocampus		−400	80	−0.81	−240	50	−0.50	.27
	Left hippocampus		−280	80	−0.57	−140	60	−0.29	.46
	Right amygdala		−50	40	−0.20	−20	30	−0.07	.80
	Left amygdala		−20	40	−0.09	−50	30	−0.19	.45
	Right nucleus accumbens		−40	20	−0.48	−10	10	−0.08	.17
	Left nucleus accumbens		−40	20	−0.48	−20	10	−0.31	.43
Model 3	Total brain		−27 830	9290	−0.21	−8540	6080	−0.07	.20
Sex	Total GM		−16 010	6090	−0.23	−9270	4070	−0.13	.41
Age	Cerebral cortical GM		−13 470	5460	−0.25	−4220	3600	−0.08	.13
Maternal smoking during pregnancy	Subcortical GM		−2510	630	−0.44	−1850	410	−0.33	.86
	Total WM		−13 260	6120	−0.20	1020	3920	0.02	.20
Maternal BMI	Cerebral WM	*	−13 750	5800	−0.21	2540	3700	0.04	.08
Maternal age	Cerebellum	†	530	2570	0.03	−4990	1650	−0.28	.04
First–born status	Ventricles		10 740	3300	1.56	9800	2250	1.42	.85
Estimated intracranial volume	Right thalamus		−680	140	−0.78	−510	90	−0.58	.55
	Left thalamus		−390	140	−0.46	−440	90	−0.52	.49
	Right caudate nucleus	†	−310	70	−0.78	−110	50	−0.27	.04
	Left caudate nucleus		−270	80	−0.69	−120	50	−0.31	.39
	Right putamen		−170	90	−0.31	−60	60	−0.11	.53
	Left putamen		−190	100	−0.34	−100	70	−0.18	.91
	Right pallidum		−40	40	−0.16	10	20	0.05	.80
	Left pallidum		−90	30	−0.37	−60	20	−0.23	.67
	Right hippocampus		−220	70	−0.45	−150	50	−0.32	.74
	Left hippocampus		−90	70	−0.19	−60	50	−0.12	.93
	Right amygdala		40	40	0.15	20	20	0.09	.47
	Left amygdala	*	60	40	0.23	−10	30	−0.03	.09

(*continued*)

Table VIII. Continued

Models and covariates		Very low birth weight + pre-eclampsia	SE	SD units	Very low birth weight, no pre-eclampsia	SE	SD units	*P* value
	Right nucleus accumbens	−10	20	−0.16	10	10	0.08	.45
	Left nucleus accumbens	−20	20	−0.21	−10	10	−0.17	.92

Fixed effects estimates (mm^3) with standard errors, SD units, adjusted for covariates. A statistical significance between the pre-eclampsia-very low birth weight and non-pre-eclampsia-very low birth weight groups.
*$P < .10$.
†$P < .05$.