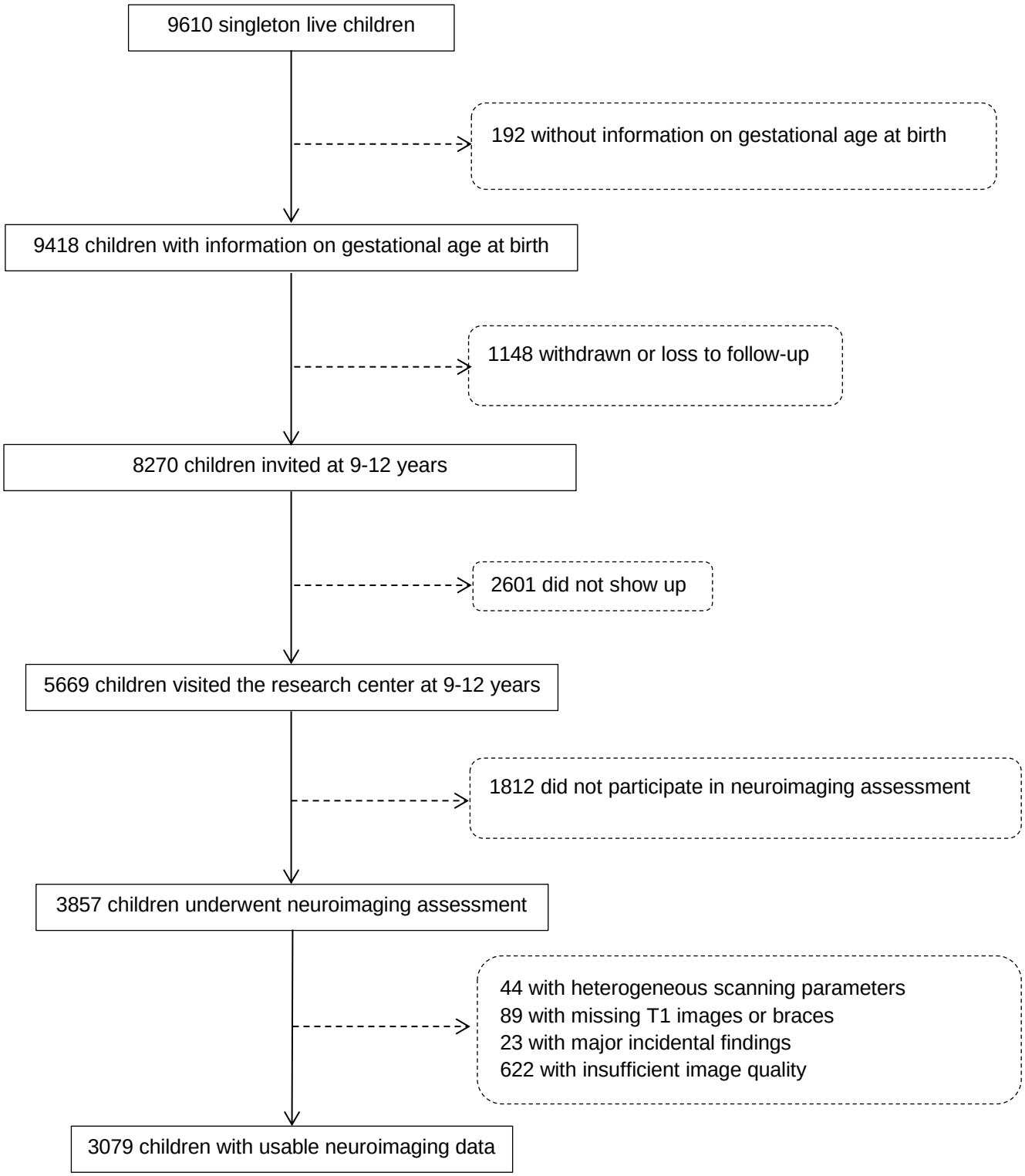
Supplementary Online Content

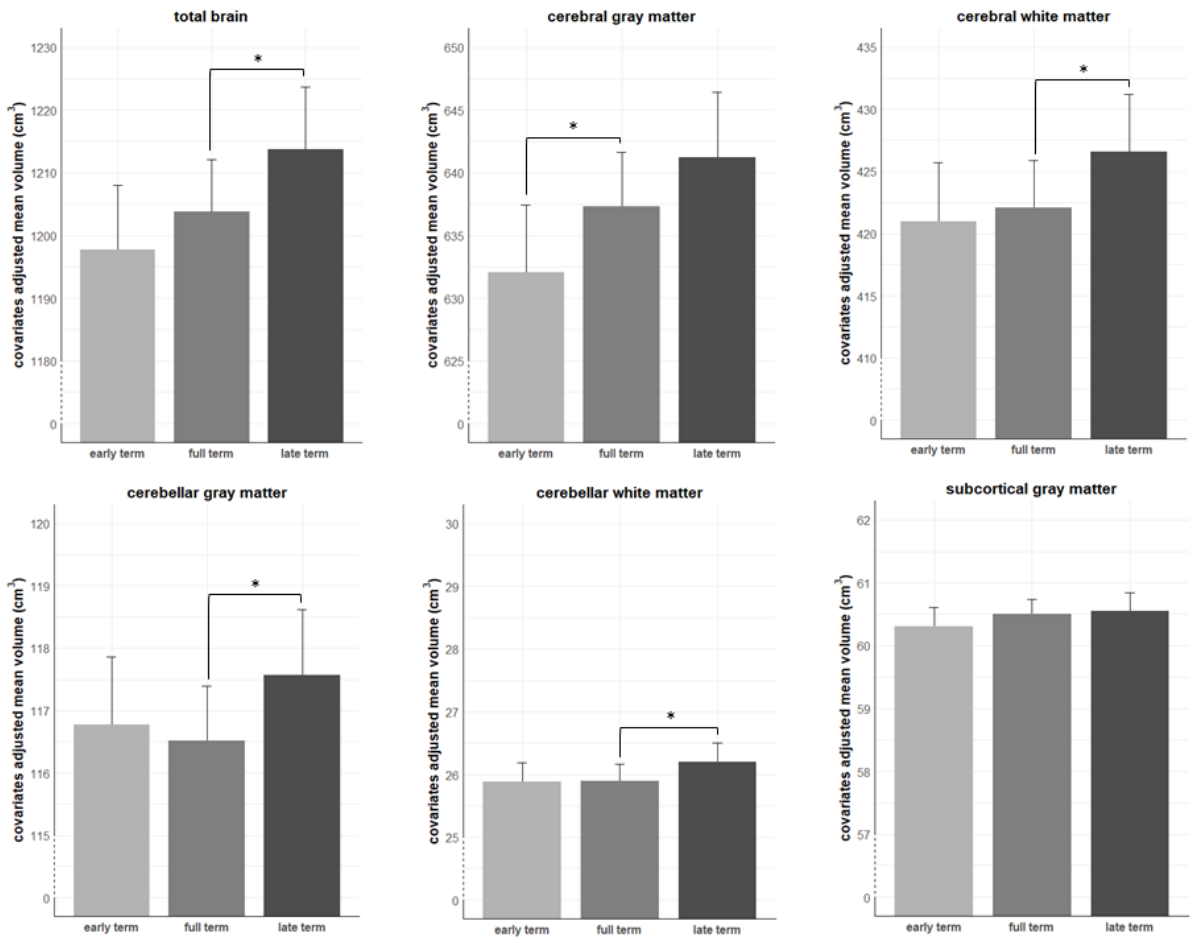
El Marroun H, Zou R, Leeuwenburg MF, et al. Association of gestational age at birth with brain morphology. *JAMA Pediatr.* Published online September 21, 2020. doi:10.1001/jamapediatrics.2020.2991

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Flow Diagram

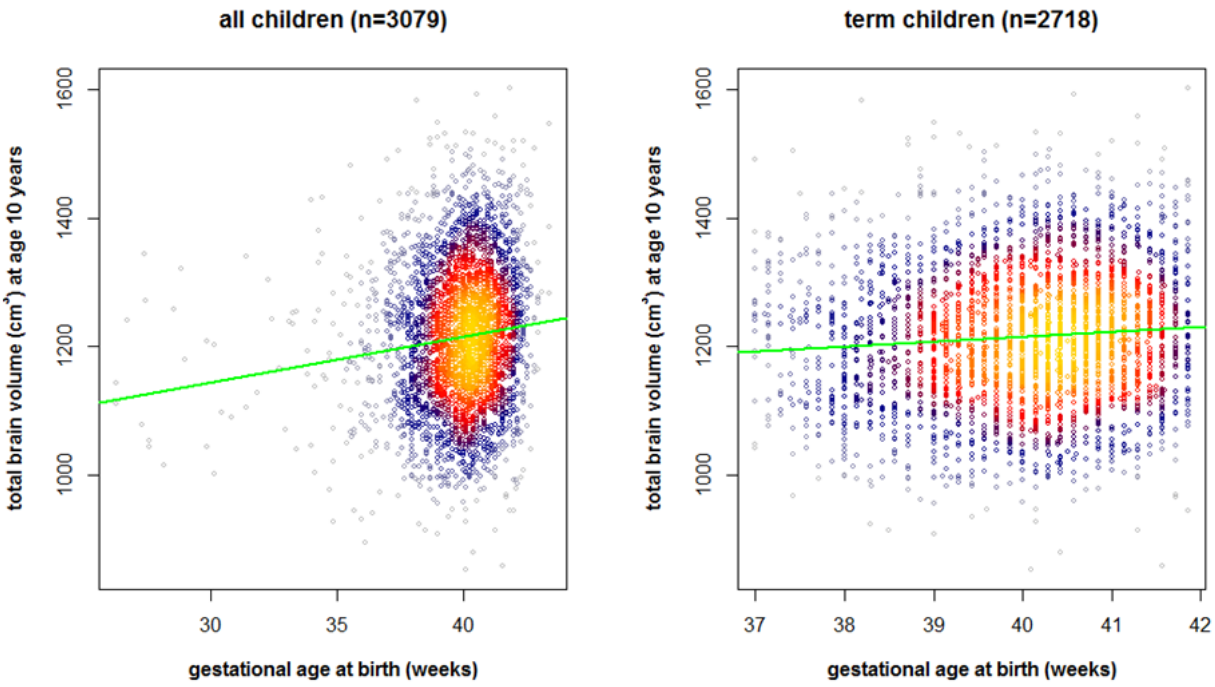


eFigure 2. Global brain volumes in children born early term, full term and late term



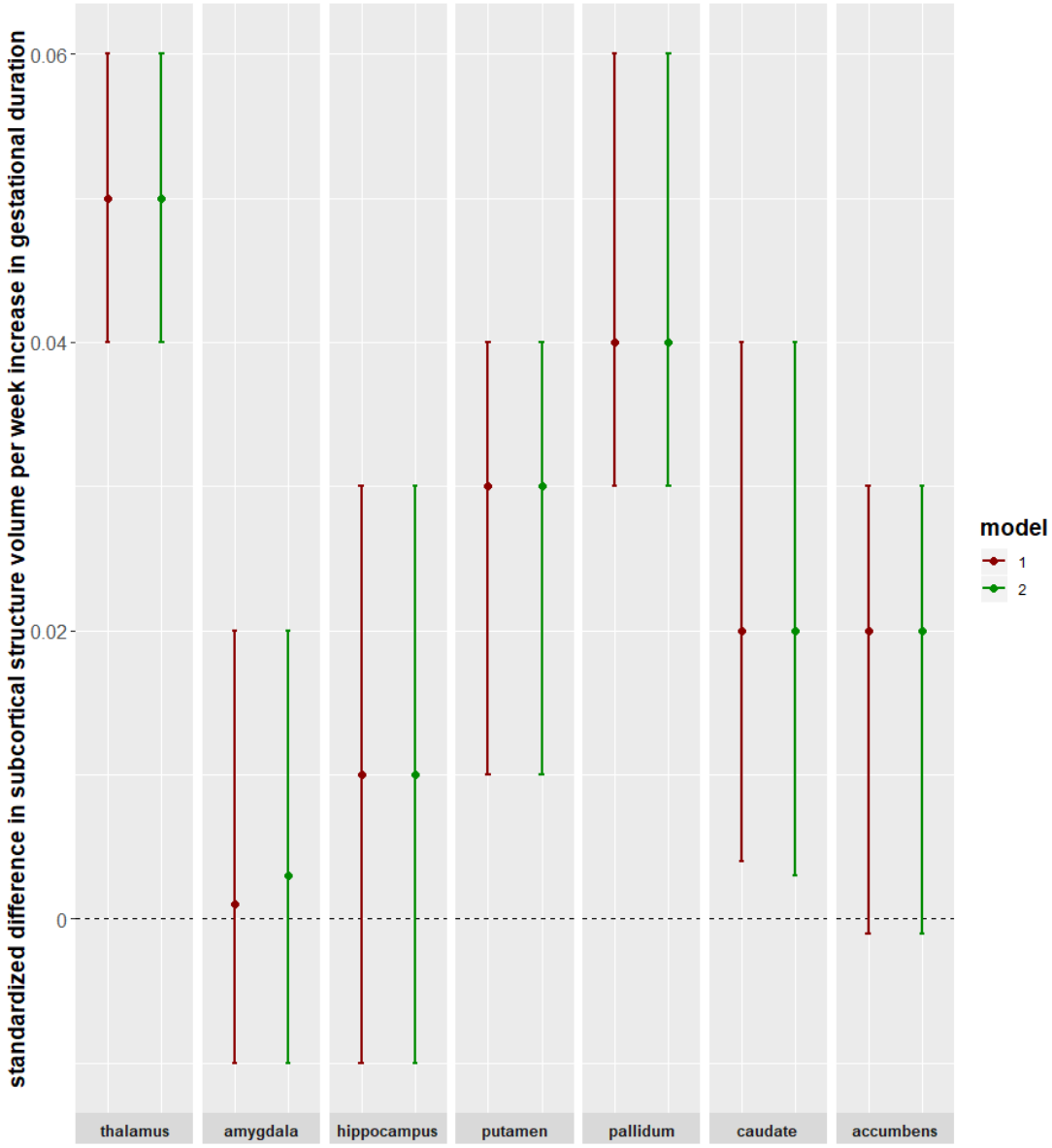
eFigure 2 legend: Brain volumes of children born at term (n=2718) are represented in three subgroups (early term, n=506; full term, n=1599; and late term, n=613). Early term are births occurring between 37 weeks 0 days and 38 weeks 6 days; full term children are those at 39 weeks 0 day through 40 weeks 6 days; late term refers to those at 41 weeks 0 day through 41 weeks 6 days. Covariates including child sex, age at MRI scan, maternal ethnicity, age at intake, marital status, educational level, psychopathology during pregnancy, smoking and alcohol use during pregnancy, and family income were adjusted. The model with subcortical gray matter as the outcome was additionally adjusted for intracranial volume. Statistical differences as indicated by the * p<.05 are comparisons of the three groups with children born full term as the reference.

eFigure 3. Linear relationship between gestational age at birth and total brain volumes in children with heatmap



eFigure S3 legend: Linear relationship between gestational age at birth and total brain volume in all children (left, n=3079) and children born at term (right, n=2718) at 10 years visualized with an additional heatmap.

eFigure 4. The association of gestational age at birth with subcortical gray matter volumes in children



eFigure 4 legend: Estimated differences (with 95% confidence intervals) in subcortical gray matter structures (in standardized z-scores) per week increase in gestational age at birth, these were computed using regression analyses in n=3079 children. Model 1 was a minimally adjusted model, corrected for child sex, age at the neuroimaging assessment, and intracranial volume. Model 2 was a fully adjusted model, corrected for child sex, age at the neuroimaging assessment, and intracranial volume, maternal ethnicity, age at intake, marital status, educational level, psychopathology during pregnancy, smoking and alcohol use during pregnancy, and family income.

eTable 1. Gestational age at birth and brain volumes at 10 years: interaction of GA with sex

Global brain volumes	statistics of GAB × sex (interaction term)		
	difference	95% CI	p-value
Total brain	0.3	-3.3 to 3.9	.88
Cerebral gray matter	0.3	-1.6 to 2.2	.74
Cerebral white matter	0.1	-1.5 to 1.8	.89
Cerebellar gray matter	-0.2	-0.6 to 0.2	.37
Cerebellar white matter	0.003	-0.1 to 0.1	.96
Subcortical gray matter *	0.01	-0.1 to 0.1	.85

The linear regression model examined the association of gestational age at birth (GAB) and global brain volumes in n=3079, in combination with an interaction term of GAB and sex. The model was adjusted for child sex and age at MRI scan, maternal ethnicity, age at intake, marital status, educational level, psychopathology during pregnancy, smoking and alcohol use during pregnancy, and family income.
* Intracranial volume was additionally adjusted for.

eTable 2. Gestational age at birth and cortical morphology at 10 years: surface-based clusters in all children

Cortical surface metric	Brain region #	Size brain region (mm^2)	Talairach coordinates			Cluster-wise p-value
			X	Y	Z	
Thickness	Left superior temporal	446.2	-45.7	6.2	-22.3	.0001
	Left superior frontal	404.0	-12.5	53.9	4.2	.0001
	Left cuneus	230.0	-5.8	-96.7	11.5	.003
	Right superior temporal	371.7	46.6	12.1	-27.1	.0001
	Right inferior parietal	171.0	33.2	-68.8	26.6	.02
Surface area	Left post central	5831.4	-58.1	-17.4	19.3	.0001
	Left inferior parietal	3132.5	-32.9	-76.5	21.4	.0001
	Left rostral anterior cingulate	2442.3	-5.3	16.9	-6.8	.0001
	Left middle temporal	2220.1	-60.8	-17.8	-16.3	.0001
	Left caudal middle frontal	1347.2	-33.3	11.2	27.2	.0001
	Left inferior temporal	937.1	-46.0	-50.6	-12.4	.0001
	Left superior parietal	403.0	-16.0	-86.0	36.5	.007
	Right middle temporal	16130.7	57.8	-16.1	-17.7	.0001
	Right inferior parietal	5130.1	34.3	-71.5	23.9	.0001
	Right fusiform	1176.6	39.5	-65.3	-15.6	.0001
	Right rostral anterior cingulate	866.8	5.4	19.6	-7.2	.0001
	Right lateral orbitofrontal	457.5	41.1	26.3	-14.6	.004
	Right medial orbitofrontal	320.0	8.7	61.5	-4.6	.02
Gyrification	Left superior parietal	27509.9	-14.6	-86.2	36.0	.0001
	Left post central	11987.8	-46.7	-11.8	17.6	.0001
	Left fusiform	642.5	-40.6	-55.4	-14.2	.002
	Right insula	35998.0	37.9	-13.7	21.5	.0001
	Right rostral anterior cingulate	4780.7	10.2	40.2	4.8	.0001

Brain regions represent colored areas in Figure 2A, 2B and 2C.
A surface-based analysis was performed in n=3065 children. The model was adjusted for child sex, age at MRI scan, maternal ethnicity, age at intake, marital status, educational level, psychopathology during pregnancy, smoking and alcohol use during pregnancy, and family income. The list of clusters represent brain regions of surface-based metrics that were associated with gestational age at birth, which surived the cluster-wise correction for multiple comparisons.

eTable 3. Gestational age at birth and cortical morphology at 10 years: surface-based clusters in children born at term

Cortical surface metric	Brain region #	Size brain region (mm^2)	Talairach coordinates			Cluster-wise p-value
			X	Y	Z	
Thickness	Left superior temporal	242.3	-41.4	8.4	-27.5	.003
Surface area	Left inferior parietal	1995.7	-30.8	-70.7	29.2	.0001
	Left lateral orbitofrontal	865.1	-11.5	58.3	-17.6	.0001
	Left middle temporal	419.4	-61.9	-35.9	-14.1	.006
	Left caudal middle frontal	345.6	-35.2	14.2	30.2	.01
	Left inferior temporal	342.8	-51.4	-42.9	-24.0	.02
	Right superior frontal	2270.4	19.4	16.8	58.2	.0001
	Right superior temporal	820.6	52.6	-26.7	-0.7	.0001
	Right frontal pole	781.9	7.8	63.7	-5.9	.0001
	Right middle temporal	672.1	63.0	-12.4	-18.5	.0002
	Right pars opercularis	535.9	50.4	8.7	1.5	.001
	Right superior parietal	458.4	10.4	-84.2	37.0	.004
	Right superior parietal	308.1	30.8	-59.0	45.2	.02
Gyrification	Left precuneus	8230.8	-7.7	-51.2	52.5	.0001
	Left post central	4942.1	-40.8	-15.9	20.7	.0001
	Left superior frontal	4024.7	-14.3	46.5	2.0	.0001
	Left inferior parietal	1138.2	-45.3	-75.9	12.5	.0001
	Left supra marginal	913.1	-56.3	-52.9	18.0	.0001
	Left fusiform	501.0	-39.4	-45.1	-19.0	.005
	Right superior parietal	9412.3	24.3	-74.1	39.9	.0001
	Right insula	8625.0	36.7	-27.0	6.2	.0001
	Right medial orbitofrontal	3335.2	9.3	56.5	-3.3	.0001

Brain regions represent colored areas in Figure 3A, 3B and 3C.
A surface-based analysis was performed in 2706 children born at term. The model was adjusted for child sex, age at MRI scan, maternal ethnicity, age at intake, marital status, educational level, psychopathology during pregnancy, smoking and alcohol use during pregnancy, and family income. The list of clusters represent brain regions of surface-based metrics that were associated with gestational age at birth, which surived the cluster-wise correction for multiple comparisons.

eTable 4. The association of gestational age at birth in categories with global brain volumes

			Total brain volume			**Cerebral gray matter volume**			**Cerebral white matter volume**		
		N	difference	95% CI	P-value	difference	95% CI	P-value	difference	95% CI	P-value
Term	Model 1	2718	ref	-	-	ref	-	-	ref	-	-
Preterm		138	-35.4	-51.6 to -19.1	<.001	-22.1	-30.7 to -13.5	<.001	-8.8	-16.1 to -1.4	.02
Post-term		223	15.0	2.0 to 28.0	.02	10.2	3.3 to 17.0	.004	3.3	-2.6 to 9.1	.28
Term	Model 2	2718	ref	-	-	ref	-	-	ref	-	-
Preterm		138	-26.5	-42.1 to -11.0	<.001#	-17.3	-25.5 to -9.1	<.001#	-5.8	-12.9 to 1.4	.12
Post-term		223	10.5	-1.9 to 22.8	.10	7.7	1.2 to 14.2	.02#	1.6	-4.1 to 7.3	.58
		N	**Cerebellar gray matter volume**			**Cerebellar white matter volume**			**Subcortical gray matter volume***		
			difference	95% CI	P-value	difference	95% CI	P-value	difference	95% CI	P-value
Term	Model 1	2718	ref	-	-	ref	-	-	ref	-	-
Preterm		138	-3.5	-5.3 to -1.8	<.001	-0.9	-1.3 to -0.4	<.001	-0.8	-1.3 to -0.4	<.001
Post-term		223	1.1	-0.3 to 2.5	.12	0.4	0.03 to 0.8	.03	0.7	0.3 to 1.0	<.001
Term	Model 2	2718	ref	-	-	ref	-	-	ref	-	-
Preterm		138	-2.6	-4.3 to -1.0	.002#	-0.8	-1.2 to -0.3	.002#	-0.8	-1.3 to -0.4	<.001#
Post-term		223	0.7	-0.6 to 2.0	.31	0.4	-0.01 to 0.7	.06	0.7	0.3 to 1.0	<.001#

In the results of these regression models, the effect estimates represent the difference in cm^3 for brain volumes in preterm or post-term born children compared to term born children. Model 1 is a minimally adjusted model corrected for child sex and age at the neuroimaging assessment. Model 2 is a fully adjusted mode, corrected for child sex and age at the neuroimaging assessment, maternal ethnicity, age at intake, marital status, educational level, psychopathology, smoking and alcohol use during pregnancy, and family income.

* Intracranial volume was additionally adjusted for in both models.

The associations survived a false discovery rate correction for multiple testing (applied tomodel 2 only).

eTable 5: Comparison of linear and non-linear (quadratic and natural cubic spline) models using the likelihood ratio test

Global brain volumes	All children (N=3079)				Term children (N=2718)		
	Linear	Quadratic	Natural cubic splines		Linear	Quadratic	Natural cubic splines
	reference	p-value	p-value		reference	p-value	p-value
Total brain	-	.33	.31		-	.25	.31
Cerebral gray matter	-	.17	.16		-	.50	.63
Cerebral white matter	-	.52	.50		-	.23	.26
Cerebellar gray matter	-	.90	.86		-	.06	.06
Cerebellar white matter	-	.26	.27		-	.26	.23
Subcortical gray matter*	-	.84	.75		-	.90	.86

In all children (n=3079) and children born at term (n=2718), non-linear models with a quadratic term or natural cubic splines were compared to linear models using likelihood ratio test. P-value <.05 would have suggested improved model fit of the non-linear models. For the natural cubic splines model the knot was set at 37 weeks (for all children) or 40 weeks (for term children). All models were corrected for child sex and age at the neuroimaging assessment, maternal ethnicity, age at intake, marital status, educational level, psychopathology, smoking and alcohol use during pregnancy, and family income.
* Intracranial volume was additionally adjusted for.

eTable 6. Non-response analysis

	Respondents (n=3079)[a]	Non-respondents (n=6339)	P-value
Maternal characteristics			
Age at intake, mean (sd), y	31.1 (4.9)	29.3 (5.5)	<.001
Multiparous (%)	11.8	16.3	<.001
Pregnancy complications (%) [b]	6.4	7.3	.14
Ethnicity (%)			<.001
Dutch	57.5	46.0	
Non-Dutch Western	12.2	11.1	
Non-Dutch Non-Western	30.3	43.0	
Educational level (%)			<.001
Primary or lower	7.2	13.8	
Secondary	41.1	48.8	
Higher	51.7	37.4	
Monthly household income (%)			<.001
< €1200 (US $1550, below social security level)	15.9	24.8	
€1200 to €2000 (US $ 1550-2580)	16.9	20.2	
> €2000 (US $ 2580, more than modal)	67.2	55.1	
Marital status, married or with partner (%)	88.2	83.9	<.001
Smoking during pregnancy (%)			<.001
Never in pregnancy	77.3	71.3	
Until pregnancy was known	8.6	8.3	
Continued in pregnancy	14.1	20.4	
Alcohol use during pregnancy (%)			<.001
Never in pregnancy	40.1	52.0	
Until pregnancy was known	13.9	12.6	
Continued in pregnancy, occasionally	36.3	29.3	
Continued in pregnancy, frequently [c]	9.7	6.1	
Psychopathology symptoms, mean (sd)	0.3 (0.4)	0.3 (0.4)	<.001
Birth and child characteristics			
Caesarean delivery (%)	12.4	12.6	.96
Suspected fetal distress (%)	7.7	7.8	.88
Apgar score at 5 min < 7 (%)	1.1	1.4	.31
Gestational age at birth, mean (sd), wk	39.9 (1.8)	39.7 (2.0)	<.001
Range	26.3-43.4	20.9-43.7	-
Birth weight, mean (sd), g	3444.8 (554.1)	3391.4 (566.9)	<.001
Male (%)	49.8	51.1	.25
Age at MRI, mean (sd), y	10.1 (0.6)	10.2 (0.8)	.68

Abbreviation: MRI, magnetic resonance imaging
Non-respondents are participants with data on gestational age at baseline, but no neuroimaging data at follow-up.
P-values were derived from t-tests for or Wilcoxon tests for continuous variables and chi-square tests for categorical variables.
a. Imputed data were reported.
b. Included occurrence of preeclampsia, diabetes, and/or pregnancy induced hypertension.
c. Frequent continued alcohol use is defined as 1 or more glasses of alcohol per week in at least 2 trimesters.