Maternal Smoking during Pregnancy and Regional Brain Volumes in Preterm Infants

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Objective To evaluate the association between maternal smoking during pregnancy and both brain volumes and head circumference in very-low-birth-weight/very-low-gestational-age infants.

Study design The PIPARI Study is a prospective follow-up study of infants with a birth weight ≤1500 g or a gestational age <32 weeks born in 2001 to 2006 (n = 232) at Turku University Hospital. The brain was imaged by serial brain ultrasound examinations until discharge and magnetic resonance imaging at term age. The head circumference was measured at birth, term, and 2 years corrected age. These measures were correlated to maternal smoking during pregnancy as reported by the mothers.

Results The prevalence of maternal smoking was 18%. The frontal lobe (P = .01) and the cerebellar (P = .03) volumes were significantly smaller in the exposed than in the unexposed infants. The volumes of the other parts of the brain did not differ. There was no association between prenatal smoking exposure and head growth or structural brain disease.

Conclusions Prenatal smoking exposure was associated with significantly smaller frontal lobe and cerebellar volumes in the brains of preterm infants. This is consistent with reports showing an association between prenatal smoking exposure and impairments in frontal lobe and cerebellar functions such as emotion, impulse control, and attention. *(J Pediatr 2010;156:185-90)*.

See editorial, p 175

Smoking during pregnancy affects the growing fetus in a number of ways. Women who smoke during pregnancy are more prone to prenatal complications,[1] including prematurity,[2,3] than nonsmokers. Smoking during pregnancy also causes intrauterine growth restriction.[4-6] The fetal lungs also mature faster if exposed to smoking, but prenatal smoking may also contribute to impaired pulmonary function and increased respiratory illnesses later on.[7,8] Newborns may have withdrawal symptoms after birth if they have been exposed to heavy smoking.[9]

Animal studies have shown that nicotine has a modifying and damaging effect on brain development.[10-12] Nicotine modulates the development of axons and synapses of the neural cell,[13] which may subsequently affect the development of the brain.[14] The maturation process of white matter is a prerequisite for normal neurologic development.[15] The effects of the other potentially toxic ingredients of tobacco smoke on the development of the fetal brain are less well known. Although fetal growth during pregnancy may be impaired because of maternal smoking, there are no solid data on its influence on the growing human fetal brain. There is evidence of increased serious long-term behavioral consequences for the offspring of smokers during pregnancy. Conditions that have behavioral manifestations such as attention-deficit hyperactivity disorder (ADHD) and neuropsychological deficits may be related to an impaired development of the brain. The effects on the individual trajectories may be robust, but the mediating factors are largely unknown. Recent evidence implies that prenatal exposure to maternal smoking modulates the development of the white matter microstructure in, for example, the frontal cortical regions and their respective neurocognitive functions.[16]

The aim of this study was to evaluate the association between smoking during pregnancy and the brain volumes at term in very-low-birth-weight (VLBW)/very-low-gestational-age (VLGA) infants. The hypothesis was that maternal smoking during pregnancy is associated with smaller brain volumes and head circumference in VLBW/VLGA infants.

ADHD	Attention deficit and hyperactivity disorder
ICC	Intraclass correlation coefficients
IVH	Intraventricular hemorrhage
MRI	Magnetic resonance imaging
VLBW	Very-low-birth-weight
VLGA	Very-low-gestational-age

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Methods

This study is a part of the multidisciplinary PIPARI Study (The Development and Functioning of Very Low Birth Weight Infants). The PIPARI Study consists of VLBW/VLGA infants born in 2001 through 2006 at Turku University Hospital. Inclusion criteria included birth weight ≤ 1500 g in a preterm infant (born below 37 gestational weeks) from 2001 to the end of 2003. From the beginning of year 2004 the inclusion criteria were expanded to include all infants below the gestational age of 32 weeks at birth even if the birth weight exceeded 1500 g. In addition, at least 1 of the parents had to speak Finnish or Swedish. A total of 293 VLBW/VLGA infants were born, and 40 (13.7%) of them died before discharge. Six infants were excluded because the language criteria were not fulfilled. Two hundred forty-seven infants were invited into the study. Eleven families refused to participate, and 4 infants moved outside the catchment area of the hospital. Altogether 232 (93.9%) eligible preterm infants participated in the study. Written consent was obtained from all parents. The PIPARI Study protocol was approved by the Ethics Review Committee of the Hospital District of the South-West Finland.

The background information and the information about smoking and alcohol consumption of the mothers during pregnancy were collected from maternal antenatal follow-up and hospital records. The question of maternal smoking is part of neonatal follow-up. It is recorded and reported nationally along with other prenatal data. In addition, before discharge, the mothers completed a questionnaire about their prenatal smoking, use of alcohol, and use of illicit drugs. Neonatal inflammatory diseases including chronic lung disease, necrotizing enterocolitis, and septicemia, were defined according to the Vermont Oxford Network definitions.[17]

Head Circumference and Brain Imaging

Head circumference was measured by use of tape-measurement of the maximal occipitofrontal circumference at birth, at term, and at 2 years of age corrected for prematurity. Serial brain ultrasound examinations were performed by the attending neonatologist, trained to do brain ultrasound examinations, in the neonatal intensive care unit at 3 to 5 days, at 7 to 10 days, at 1 month of age, and then monthly until discharge from the hospital.

Magnetic resonance imaging (MRI) was performed at term of corrected age. The imaging took place during postprandial sleep without pharmacologic sedation or anesthesia. The MRI equipment was either an open 0.23 Tesla Outlook GP (Philips Medical Inc., Vantaa, Finland) for the first 126 investigations or 1.5 Tesla Philips Gyroscan Intera (Philips Medical Systems, Best, The Netherlands) for the remaining 106 infants. A total of 209 of 232 magnetic resonance investigations were successfully performed. For volume measurements, at 0.23 T we obtained a T_1-weighted field echo sequence with a time repetition of 30 msec, a time echo of 10 msec, a flip angle of 45 degrees, a slice thickness of 5 mm, a field of view of 220 × 220 mm^2, and a matrix of 256 × 256 was obtained in the coronal plane. At 1.5 T we obtained a coronal T_1-weighted inversion recovery sequence with a time repetition of 3500 msec, a time echo of 400 msec, a time inversion of 15 msec, a flip angle of 90 degrees, a slice thickness of 4.8 mm, a field of view of 180 × 180 mm^2, and a matrix of 256 × 256. The sequences were optimized relative to the field strength of the equipment used.

The postacquisition volume measurements were performed on a GE workstation (GE AW1.0, GE Medical Imaging Systems, Milwaukee, Wisconsin). The coronal T_1-weighted images were loaded into Functool 1.0 post-processing software (GE Medical Systems). Volume measurement was manually performed separating cerebrospinal fluid and the skull from brain tissue. Anatomic differentiation of the brain areas was based on both the anatomic landmarks and on signal intensity differences of the brain structures. In addition to the total brain volume (total brain volume excluding ventricle volumes), the regional brain volumes measured were the cerebral volume, the cerebellar volume, the frontal lobe volume, the combined volume of the medulla oblongata and the pons, and the combined volume of the basal ganglia and the thalami. The cerebellar volume included the cerebellar hemispheres, the vermis, and the cerebellar pedunculi. The frontal volume included the frontal lobes anterior to the central sulcus, excluding basal ganglia and lateral ventricles. The pons and medulla oblongata area were delineated together, with the upper border being the lower border of the mesencephalon and the lower border being the junction between the medulla oblongata and the cervical spinal cord. The basal ganglia and thalami were measured as a block, and the anatomic border between these basal grey matter nuclei and unmyelinated deep white matter on both field strength images was easily delineated by visual inspection. The medial border of the basal ganglia and the thalami was formed by the third ventricle, the lateral border was formed by the external capsule, and the inferior border was formed by the upper border of the mesencephalon. The classification of intraventricular hemorrhage (IVH) was done as described by Papile et al.[18] Structural brain disease was categorized into normal, minor, and major pathology group (definitive brain pathology) according to the most pathologic brain finding either with ultrasonography or MRI.[19]

The brain volume measurements of all the infants in this study were performed by 1 neuroradiologist (R.P.) blinded to the clinical data. The reproducibility of the brain volume measurements was assessed by repeated brain volume measurement of 20 infants, performed by another neuroradiologist who was blinded to the clinical data and the results of the first volume measurement. The intraclass correlation coefficients (ICC [2,1])[20] were calculated to describe the reliability of the brain volume measurements. The ICC ranged from 0.93 to 0.99, except for the volume of brainstem for which the ICC was 0.78. The ICC was 0.95 for the volume of the cerebellum and 0.99 for the frontal lobe. In addition, we calculated the ICC of the volume of the frontal lobe and the cerebellum separately for the 0.23 T and 1.5 T MRI

equipment. The ICC of the volume of the frontal lobe was 0.96 with the 0.23 T MRI equipment and 1.00 with the 1.5 T MRI equipment. The ICC of the volume of the cerebellum was 0.94 and 0.95, respectively.

Statistical Analysis

The confounding factors were considered to be the infant's gestational age at birth, the weight SD at birth, sex, patent ductus arteriosus, IVH, combined chronic lung disease, necrotizing enterocolitis, and septicemia as neonatal inflammatory disease, MRI equipment, and the mother's alcohol consumption during pregnancy. IVH was categorized as mild (including grades I and II) to severe (including grades III and IV). The volumes of ventricles and brainstem were log transformed before data analysis because they were positively skewed.

The independent samples *t* test was used to compare brain volumes between the infants unexposed or exposed to prenatal smoking. Subsequently, analysis of covariance was used to further study associations between smoking and brain volumes controlling for confounding factors. Associations between brain volumes and number of cigarettes smoked were studied by use of regression analysis. A mixed-model repeated measures analysis with an unstructured covariance matrix was used to study associations between the head circumference and predictor variables. In the first model, the independent variables were age, smoking, and interaction between age and smoking. Then, the second model was estimated in which the confounding variables were added to the first model. The effect of maternal smoking on the brain pathology of the infants (normal/minor/major) was analyzed with the Mantel-Haenszel χ^2 test. The data analysis was performed with SAS (version 9.1; SAS Institute, Cary, North Carolina). A *P* value of <.05 was considered statistically significant.

Results

A total of 42 (18.1%) mothers of 232 smoked during pregnancy. Of these mothers, 38 (90.5%) reported the number of smoked cigarettes per day (Table I). The median was 10 cigarettes smoked per day.

The frontal lobe volumes were significantly smaller in the VLBW/VLGA infants exposed to prenatal smoking than in the VLBW/VLGA infants whose mothers did not smoke during pregnancy ($P = .03$; Table II). The difference remained significant after adjusting for confounding factors ($P = .01$). The cerebellar volumes were significantly smaller after adjusting for confounding factors ($P = .03$). The volumes of the total brain tissue, the cerebrum, the ventricles, the brainstem and the combined volume of basal ganglia and thalami did not differ between the 2 groups. There was no significant dose relationship between the number of cigarettes smoked and the brain volumes.

A subgroup analysis of infants below 32 gestational weeks did not affect the main results. In a subgroup analysis of infants with a birth weight at or below 1500 g, the frontal lobe volume remained significantly smaller in infants exposed to prenatal smoking, but the cerebellar volumes were not statistically significantly different between the exposed and unexposed infants ($P = .06$). There was no association found between maternal smoking and structural brain disease ($P = .75$) nor between maternal smoking and head circumference at any of the age points in VLBW/VLGA infants after adjusting for confounding factors ($P = .12$; Table III).

Table I. Background factors in infants exposed and unexposed to prenatal smoking

Characteristics	Exposed (n = 42)	Unexposed (n = 190)	*P* value
Sex			
Male	28 (66.7)	103 (54.2)	
Female	14 (33.3)	87 (45.8)	.14
Gestational age, wk x/7 d			
Mean (SD)	29 1/7 (2 6/7)	29 0/7 (2 5/7)	
Min, Max	24 0/7, 36 1/7	23 0/7, 35 6/7	.86
SD of weight at birth*			
Mean	-1.43 (1.61)	-1.40 (1.50)	
Min, Max	-4.70, 2.00	-4.90, 3.40	.91
Cigarettes per day†			
0	0 (.0)	190 (100.0)	
1-10	25 (65.8)	0 (.0)	
11-20	8 (21.1)	0 (.0)	
>20	5 (13.2)	0 (.0)	.01
Neonatal inflammatory disease‡			
No	32 (76.2)	129 (68.3)	
Yes	10 (23.8)	60 (31.7)	.31
PDA†			
No	37 (88.1)	162 (87.1)	
Yes	5 (11.9)	24 (12.9)	.86
IVH§			
No	30 (71.4)	147 (78.2)	
Mild	9 (21.4)	28 (14.9)	
Severe	3 (7.1)	13 (6.9)	.57
MRI equipment			
0.23 Tesla	22 (52.4)	103 (54.2)	
1.5 Tesla	20 (47.6)	87 (45.8)	.83
Mother's alcohol use			
No	35 (83.3)	179 (94.2)	
Yes	7 (16.7)	11 (5.8)	.03
Mother's illicit drug use			
No	40 (95.2)	189 (99.5)	
Yes	2 (4.8)	1 (.5)	.08

PDA, Patent ductus arteriosus; *NEC,* necrotizing enterocolitis; *CLD,* chronic lung disease.
Values are numbers (percentages) unless stated otherwise
*Standard deviation of birth weight from the mean according to Finnish growth charts.
†Missing information for 4.
‡Neonatal inflammatory diseases including septicemia, NEC, and CLD. Missing information for 1.
§Missing information for 2.

Discussion

We have shown that the frontal lobe and cerebellar volume of the brain were significantly smaller in preterm VLBW/VLGA infants who were exposed to prenatal smoking than in unexposed infants when confounding factors were considered. Prenatal smoking exposure was not associated with structural brain disease or early head growth.

Prenatal nicotine exposure evokes postnatal central nervous system cell loss, and the frontal lobe and the cerebellum seem to be vulnerable. Among human beings, the pathomechanisms of

Table II. Prenatal exposure to smoking and regional brain volumes at term

	Exposed (n = 38)		Unexposed (n = 171)		*P* value in univariate analysis	*P* value in multivariate analysis*
	Mean (SD)	Min, max	Mean, (SD)	Min, max		
Cerebrum (mL)	361.7 (47.2)	271.0, 464.9	367.6 (48.3)	233.0, 479.8	.50	.13
Frontal lobe (mL)	117.9 (18.9)	85.0, 160.0	127.3 (24.7)	67.0, 194.1	.03	.01
Basal ganglia and thalami (mL)	24.4 (3.8)	17.1, 33.9	25.3 (4.9)	13.0, 42.8	.26	.17
Cerebellum (mL)	23.1 (5.3)	9.0, 34.0	24.5 (5.0)	5.7, 37.8	.12	.03
Brainstem (mL)	6.0 (2.2)	3.9, 12.1	6.4 (2.6)	2.5, 14.9	.59	.63
Total brain volume (mL) (ventricles excluded)	390.8 (51.3)	289.0, 498.9	398.4 (51.2)	254.0, 514.9	.41	.09
Ventricles (mL)	17.0 (35.2)	3.0, 222.9	14.1 (14.5)	2.3, 138.3	.72	.78

*Adjusted for infant's gestational age at birth, the weight SD at birth, sex, patent ductus arteriosus, IVH, neonatal inflammatory diseases, MRI equipment, and mother's alcohol consumption during pregnancy

the effects of maternal smoking are not yet well known. On the basis of rat models, Trauth et al[21] suggested that one mechanism could be overexpression of c-Fos in the forebrain, the cerebellum, and the brainstem after prenatal nicotine exposure. C-Fos is a nuclear transcription factor that is involved in cell differentiation and cell death. Interestingly, Chen et al[22] showed that nicotine-exposed rats have a lighter forebrain, but there was no association between nicotine exposure and the weight of the other parts of the brain. Orbitofrontal, middle frontal, and parahippocampal cortexes were reported to be thinner in children aged from 12 to 18 years who were exposed to prenatal smoking.[23] Furthermore, in a group of long-term adult smokers, magnitude of lifetime smoking exposure was associated with reduced cerebellar, frontal, and temporal lobe volumes.[24] Altogether, the available literature suggests that the frontal lobe and cerebellum are the most vulnerable brain regions for nicotine, and their volume loss is a sensitive indicator for a prolonged prenatal exposure.

ADHD has been shown to relate to decreased brain volume, especially the total cerebellar volume after adjusting for the total brain volume.[25] Reduced brain volumes have also been shown in the frontal region,[26,27] in children aged from 5 to 18 years with ADHD compared with healthy age- and sex-matched children. The cerebellar vermal volume has also been associated with ADHD.[28] Middleton and Strick[29] indicate that the cerebellum influences the frontal region via the thalamus in primates, and it involves many aspects of cognitive behavior. In adults with ADHD compared with healthy adults, there were brain activation deficits and connectivity changes in prefrontal and cerebellar regions during cognitive processing.[30] In addition, children with ADHD showed delayed cortical maturation, especially in the frontal region compared with healthy control subjects.[31] Interestingly, Cao et al [32] showed in a functional MRI study that the frontal, parietal, and putamen regions displayed less activation in children with ADHD aged from 11 to 16 years compared with the control children. Furthermore, prenatal smoking exposure has been connected with an increased risk of ADHD in children.[33-36] Our results, showing smaller frontal lobe and cerebellar volumes of the brain in preterm infants exposed to prenatal smoking, suggest that reduction of the frontal and cerebellar brain tissue could be the mechanism connecting prenatal smoking to later risk for ADHD. There are also other behavioral disorders, such as impairments of impulse and emotion control connected to the frontal lobe dysfunction[37] that might be related to prenatal smoking exposure.

Our study has several strengths. The study population consisted of a regional cohort of preterm VLBW/VLGA infants and the recruitment and follow-up percentage was high. We could perform detailed MRI analysis, including brain volumes. In addition, a wide range of different confounding factors is a significant strength of our study. Alcohol as a confounding factor is important because alcohol exposure during pregnancy leads to smaller head circumference and reduced brain volumes, for example, total parenchymal and hippocampal volume in offspring.[38,39]

There were also limitations to our study. There might be background factors associated with smoking that were not asked or gathered. Maternal smoking history was based on self-reporting, which is known to give an underestimation of the true amount of smoking.[40,41] In this study, samples for objective analyses of nicotine metabolites were not collected. However, the rate of smoking (18%) in our study was at the same level as the prevalence of smoking during pregnancy in the whole country (15%).[42] These results may not be applicable

Table III. Prenatal exposure to smoking and head circumference at birth, at term, and at 2 years CA

	Exposed			Unexposed				
Age	No.	Mean (SD), cm	Min, max, cm	No.	Mean (SD), cm	Min, max, cm	Unadjusted *P* value	Adjusted *P* value*
At birth	42	26.3 (2.8)	20.7, 31.1	190	26.5 (2.6)	20.0, 32.0		
At term	42	34.3 (1.9)	29.5, 37.5	188	34.6 (1.6)	29.0, 39.5	.25	.10
At 2 years of CA	38	48.4 (2.1)	42.0, 53.1	185	48.9 (1.7)	44.3, 53.8		

CA, Corrected age.
*Adjusted for infant's gestational age at birth, the weight SD at birth, sex, patent ductus arteriosus, IVH, neonatal inflammatory diseases, and mother's alcohol consumption during pregnancy.

to full-term infants because our study was focused on preterm infants. Full-term infants may be even more vulnerable to prenatal exposure to smoking because they have been exposed to smoking for a longer period of time during pregnancy. This is supported by the findings showing smaller head circumference in exposed full-term infants,[5,38,43] which was not seen in our preterm cohort. This suggests that full-term infants may have more global brain volume reduction after prolonged prenatal smoking exposure.

There were only 5 infants whose mothers smoked more than 20 cigarettes per day. The small number of heavy smokers may explain the lack of dose relationship in this study. It is of interest that even with a relatively low average amount of smoking, we found a significant correlation between prenatal smoking and the frontal lobe and cerebellar volumes of the brain.

In spite of growing awareness of the deleterious fetal effects of smoking, smoking during pregnancy has remained common.[42] Therefore it is an important challenge for antenatal care to recognize smoking mothers and to encourage smoking cessation. Nicotine replacement therapy has been both advocated and criticized during pregnancy.[44]

In the future, the relationship between smoking during pregnancy and brain volumes should also be studied in full-term infants. It would be especially interesting to study the executive functions of the brain by use of functional MRI in prenatally exposed and unexposed infants. The reduced frontal lobe and the cerebellar volumes also give a reason to suggest that later psychiatric disorders might be more common in exposed individuals.

In conclusion, prenatal exposure to maternal smoking associates to the frontal lobe and cerebellar volumes in prematurely born infants. This may partly explain the association between prenatal smoking exposure and the increased risk for ADHD and other behavioral problems.[33,45,46] ■

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Appendix

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