These findings reveal that maternal smoking during pregnancy adversely affects neurobehavioral development of offspring in their neonatal period, but that it does not affect offspring after their infancy, suggesting that the postnatal child rearing environment has a great influence on child development.

Keyword: *maternal smoking, neurobehavioral development, home environment, socioeconomic status.*

Introduction

The number of cigarette smokers in Japan declined during the 1990s but female smokers, especially young women and women of child-bearing age, have increased [1]. The number of women smoking during pregnancy has also increased. For instance, the Japan Ministry of Health, Labour and Welfare reported that the percentage of women who smoked during pregnancy was 5.6% in 1990, and increased to 10.0% in 2000 [2]. Thus cigarette smoking among women, especially smoking during pregnancy, continues to be a significant public health concern in Japan.

The biological mechanisms that govern the effects of maternal smoking on fetal and infant development are potentially complex, given that cigarette smoke has over 2,000 chemical constituents, most at trace levels [3]. Well-documented constituents of cigarette smoke are carbon monoxide and nicotine, both of which are neurotoxins in various species [4]. Several mechanisms, direct and indirect, have been proposed to explain the effects on fetuses and infants. The indirect effects of cigarette smoking on the fetus include blood flow restriction to the placenta due to the vasoconstrictive effects of catecholamines released from the adrenals and nerve cells after nicotine activation. Direct effects result from the interactions of nicotine with nicotinic acetylcholine receptors that are present very early in the fetal brain [5]. In addition, products of cigarette smoke (e.g., carbon monoxide and ingredients in tobacco tar) can affect the fetal brain [6].

Maternal smoking is well known to have various effects on the fetus and infant. Children of smoking mothers are often born with lower birth weight or shorter gestational age [7][8]. In addition, there is an increase in the risk of premature labour, intrauterine growth retardation, and perinatal mortality as the result of cigarette use in the prenatal period [9].

Several studies demonstrated the adverse effects of maternal smoking during pregnancy on neurobehavioral status in the neonatal period. In these studies, newborns whose mothers smoked during pregnancy showed more stress signs, increased tremulousness and lower motor and habituation scores [10][11][12][13][14][15]. These effects remain after control for maternal characteristics, including alcohol use. However, the effects of maternal smoking during pregnancy have been less consistent in studies of children in their infancy. Several studies have demonstrated a relationship between maternal smoking during pregnancy and delays in childrens' subsequent cognitive development. In a study of more than 40,000 pregnant women, a relationship was found between maternal smoking and low scores on the Bayley Scales of Infant Development (BSID) in children 8 months of age [16]. Fried et al. (1988) [17] found that maternal smoking during pregnancy was associated with a lower

mental index on the BSID when children were 1 year of age, controlling for maternal education and environmental factors; however, they also reported that the BSID at 2 years of age had no relation to maternal smoking after controlling for environmental factors. In a study that followed children from birth to 4 years of age, lower scores in children of smokers could be explained by differences in socioeconomic status (SES), the mother's intelligence and the degree of stimulation received by the child [18]. Other studies found that maternal smoking had no effect on the BSID in the childrens' first year of life [19][20][21].

The BSID was used in many early studies to examine the effects of maternal smoking on cognitive development in infancy. Some studies established that there were negative associations between maternal smoking during pregnancy and cognitive development of the offspring; other studies, on the other hand, did not find any association between the two. Thus, the effects of maternal smoking on cognitive development in infancy remain unclear. The influence of a variety of postnatal environmental factors such as the quality of the home environment and the SES, is thought to be a reason for this inconsistency. During the neonatal period, the effects of maternal smoking on neurobehaviroral development might be detectable because environmental factors have less influence on child development. Because the effects of maternal smoking on offspring development are thought to be small, they might be hard to detect when masked by postnatal environmental factors strongly related to child development. It is necessary to take the possible interaction of postnatal environmental factors such as the quality of the home environment and the SES on offspring development into consideration when examining the effects of maternal smoking during pregnancy on the development.

In the Tohoku Study of Child Development (TSCD), ongoing longitudinal prospective cohort study, the effects of perinatal exposure to environmentally persistent organic pollutants and heavy metals on child development are being examined [22]. Previously, using the data of the TSCD, we studied the association between maternal smoking during pregnancy and neonatal neurobehavioral status, and found that children whose mothers smoked during pregnancy showed lower scores than those of ex-smokers and nonsmokers on several behavioral items of the Neonatal Behavioral Assessment Scale (NBAS) [23]. In the present study, the association between maternal smoking during pregnancy and neurobehavioral development of offspring was readdressed; the neurobehavioral and cognitive development of children at 3 days, 7 months, and 18 months of age were assessed with the NBAS, the Fagan Test for Infant Intelligence (FTII), and the BSID 2nd edition (BSID-II), respectively. We gave special consideration to postnatal environmental factors such as the quality of the home environment, the SES, and the mother's IQ, to examine associations between maternal smoking during pregnancy and the neurobehavioral and cognitive development of offspring.

Methods

Participants

The 286 mother-child pairs who took part in the present study were participants in the TSCD study [22] who provided information on smoking habits, mother's IQ, the quality of the home environment, the duration of breast feeding and the SES. The children, who consisted of 147 boys and 139 girls, also underwent neurobehavioral assessments at 3 days, 7 months, and 18 months of age. All children were born at full-term (36-42 weeks of gestation), without congenital anomalies or diseases, and with birth weights of over 2400 gm. All procedures were approved by the Medical Ethics Committee of the Tohoku University Graduate School of Medicine, and informed consent was obtained for all participants.

Maternal Smoking Habits and Other Factors

Maternal smoking habits were assessed using a self-administered questionnaire 4 days after delivery. Smoking habits were classified into 4 categories: (1) Never smoked, (2) Ceased to smoke in the past, (3) Ceased smoking during pregnancy, and (4) Smoked throughout pregnancy. When the statistical analyses were conducted, mothers were classified into 3 groups according to their smoking habits based on the questionnaire; nonsmokers, including (1) and (2); ex-smokers, who checked (3); and smokers, who checked (4).

Information about mother's demographic factors such as educational status and alcohol use was collected 4 days after delivery. Questions about the presence of smokers in the family other than the mother in the postnatal period, the mother's IQ, quality of the home environment, SES, and the duration of breast feeding, were posed to the mother when the child was 18 months of age. The mother's IQ was measured using the Raven Standard Matrices [24]. Since the Japanese version of the Raven Colored Progressive Matrices has been standardized for people over 40 years of age [25], we used the original version and analyzed the results using the raw score. The quality of the home environment was assessed using a self-administered questionnaire, the Evaluation of Environmental Stimulation (EES) [26], which has been established in Japan and modified after the Home Observation for Measurement of the Environment (HOME) score [27]. The EES consists of 40 items classified into 8 categories: opportunities for variety in daily stimulation, emotional and verbal responsiveness, avoidance of restriction and punishment, maternal acceptance of the child, provision of appropriate play materials, maternal involvement with the child, organization of the physical and temporal environment, and the presence of social support for child rearing. The SES was evaluated using the annual household income. Mothers and fathers were classified into 8 scoring categories based on their respective annual incomes: 0, none; 1, < 1 million yen; 2, 1-3 million yen; 3, 3-6 million yen; 4, 6-9 million yen; 5, 9-12 million yen; 6, 12-30 million yen; and 7, > 30 million yen. The annual household income was taken as the sum of the incomes of both parents. The duration of breast feeding was classified into 4 categories based on whether the child was still breast fed at 2, 4 or 6 months of age: 1, < 2 months; 2, 2-4 months; 3, 4-6 months; and 4, > 6 months.

Measurements for Neurodevelopment

All neurobehavioral assessments were carried out by trained examiners who had no knowledge of the maternal smoking habits. The neurobehavioral status of neonates was examined with the Neonatal Behavioral Assessment Scale (NBAS) [28] when the children were 3 days of age. The scale combines neurological items with an extended behavioral repertoire of the neonates in an interactional process [29]. The basic score is composed of 28 behavioral items and 18 reflex items. To compare the evaluations of the neonatal behavior, all items, excepted for behavioral item 'smiling', that interact in similar ways have been classified into 7 clusters describing global functions [30]. Higher scores in behavioral items and clusters indicate a better behavioral response, whereas higher scores for the reflex cluster score indicate a more abnormal response. The visual recognition memory in infancy was examined using the Fagan Test for Infant Intelligence (FTII) [31] when the children were 7 months of age. The child, seated on the mother's lap, was first shown two identical photos (face) and then a novel photo paired with the familiar one. The normative response at this age is to look longer at the novel photo. Preference for the novel stimulus indicates the ability to recall the familiar stimulus and discriminate it from the novel one. The child's fixation was recorded on a computer, and the preference for novelty was computed by dividing the duration of the time looking at the novel stimulus by the total amount of time spent looking at the paired familiar and novel stimuli for each of the 10 tasks. Preferential looking is believed to reflect more rapid processing of visual information and has been found to relate to performances on several intellectual tests in childhood [32]. The Bayley Scales of Infant Development second edition (BSID-II) [33] were employed when the children were 7 months and 18 months of age. The BSID-II is one of the most frequently used standardized tests of infant function, and consists of the Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI).

Statistical Analysis

For variables with normal distribution, one-way analysis of variance (ANOVA) was used to compare mean values. When a difference was detected, the HSD test was used as a post-hoc test. For variables without normal distribution the Kruskal-Wallis test was used. For the categorical variables the χ^2 test was used. On the NBAS, 7 clusters and 27 behavioral items, with the exception of the behavioral item 'smiling', were used for analysis. On the FTII, % of time looking at a novel target was used for analysis. On the BSID-II, the MDI and the PDI were used for analysis.

For comparisons of measurements of neurodevelopment, we also used the general linear model (GLM) to calculate adjustment for potential covariates. The HSD was used as a post-hoc test. Potential covariates were selected from demographic and medical characteristics (Table 1), and were included based on the criteria that the covariates were correlated ($r > 0.2$) with smoking or outcome and were not highly correlated ($r < 0.7$) with each other. Based on these criteria the covariates selected were the presence of a smoker in the family (during pregnancy or postpartum), mother's educational status, sex and birth weight. All analyses were done using the statistical program SPSS 13.0 J (SPSS Inc, Japan).

Results

Maternal Smoking Status

Ten of the 286 (3.4%) mothers smoked throughout their pregnancy. Of the 278 mothers who did not smoke, 42 were ex-smokers and 236 were nonsmokers. Smokers reported that they smoked an average of 14.0 (SD 6.6) cigarettes per day during pregnancy.

Mothers' and Children's Characteristics

Table 1 shows the mothers' and children's characteristics. Mothers of the smoking group had lower Raven scores than the other 2 groups ($F_{(2, 283)} = 10.0$, $p < 0.01$), and had a lower educational status ($\chi^2_{(2)} = 13.0$, $p < 0.01$). For maternal alcohol drinking during pregnancy, the smokers had a higher rate than the other 2 groups ($\chi^2_{(2)} = 8.6$, $p < 0.05$). The family smoking group had a high rate of smoking in the pregnancy ($\chi^2_{(2)} = 8.6$,, $p < 0.05$) and also postnatally ($\chi^2_{(2)} = 8.6$, $p < 0.05$). The smokers breastfed for a shorter duration than the other 2 groups ($F_{(2, 283)} = 5.9$, $p < 0.01$), and had a lower EES score ($F_{(2, 283)} = 3.3$, $p < 0.05$). The biological characteristics of the children did not differ among the 3 groups of mothers.

Table 1. Mothers' and children's characteristics

	Smoking during pregnancy				
	No		Yes		
	Nonsmoker (n = 234)	Ex-smoker (n = 42)	Smoker (n = 10)		
	M (SD)	M (SD)	M (SD)	F	χ^2
Maternal age at delivery (y)	31.7 (3.9)	29.5 (5.2)	30.8 (3.4)	8.18**	
Education (% > 12y)	79.5	57.1	50.0		13.05**
Alcohol drinking in pregnancy (% yes)	22.5	33.3	60.		8.62*
Delivery order (% first)	50.0	42.9	50.0		0.73
Delivery type (% Caesarian)	15.4	16.7	40.0		4.23
Presence of smokers in family during pregnancy (% yes)	44.9	85.7	100		33.10**
# Presence of smokers in family postnatal (% yes)	39.7	90.5	100		47.32**
# Raven score	53.3 (4.3)	50.9 (5.2)	48.4 (5.2)	10.05**	
# Duration of breast feeding	3.6 (0.8)	3.2 (0.9)	2.9 (1.2)	5.93**	
# EES score	30.4 (3.8)	28.9 (3.1)	28.8 (3.3)	3.28*	
# Income of household	4.4 (1.6)	3.9 (1.7)	3.8 (1.5)	2.12	
Sex (% male)	52.1	45.2	60.0		0.99
Gestational age (w)	39.5 (1.4)	39.8 (1.0)	39.6 (1.2)	0.67	
Birth weight (g)	3048 (337)	3126 (327)	2994 (363)	1.15	
Birth length (cm)	49.0 (1.8)	49.2 (1.6)	48.8 (2.1)	0.38	
Apgar score 1 min after delivery	8.2 (0.8)	8.2 (0.5)	8.1 (0.6)	0.15	

*$p < 0.05$ ** $p < 0.01$

These items were investigated at the age of 18 months. For comparisons among groups, ANOVA or the Kruskal-Wallis test was used for continuous variables, and the χ^2 test was used for categorical variables.

Table 2. Maternal smoking and the NBAS

Cluster	Non-smoker	Ex-smoker	Smoker	*F*	
Behavioral Item	M (SD)	M (SD)	M (SD)	Unadjusted	Adjusted
Habituation	6.7 (1.6)	6.6 (1.4)	6.6 (2.0)	0.08	0.06
Response decrement to light	6.3 (1.9)	6.3 (1.9)	5.2 (2.7)	1.48	1.05
Response decrement to rattle	7.2 (2.1)	6.9 (2.3)	7.4 (1.7)	0.49	0.46
Response decrement to bell	7.5 (1.8)	7.8 (1.5)	8.0 (2.0)	0.52	0.45
Response decrement to foot stimulation	6.2 (2.3)	5.6 (2.5)	6.9 (2.7)	1.24	1.46
Orientation	4.4 (1.0)	4.3 (1.3)	4.2 (1.5)	0.31	0.19
Animate visual	4.4 (1.2)	4.2 (1.2)	4.3 (1.4)	0.47	0.11
Animate visual and auditory	4.8 (1.2)	4.6 (1.3)	4.5 (1.4)	0.76	0.27
Inanimate visual	3.8 (1.2)	3.9 (1.6)	3.7 (1.5)	0.23	0.30
Inanimate visual and auditory	4.8 (1.4)	4.7 (1.8)	4.3 (1.3)	0.44	0.53
Animate auditory	4.4 (1.6)	4.2 (1.7)	3.3 (1.9)	1.84	1.23
Inanimate auditory	4.4 (1.2)	4.4 (1.4)	3.8 (1.6)	0.99	1.00
Alertness	4.2 (1.1)	4.2 (1.4)	4.3 (1.7)	0.07	0.13
Motor	4.7 (0.6)	4.7 (0.7)	4.4 (0.7)	1.09	1.26
General tone	5.1 (1.0)	5.0 (1.1)	5.0 (0.9)	0.18	0.11
Motor maturity	4.3 (1.1)	4.6 (1.2)	4.9 (1.1)	2.62^{+}	1.33
Pull to sit	5.2 (1.0)	5.0 (1.2)	4.4 (1.3)	2.93^{+}	3.57*[a]
Defensive movements	4.7 (1.6)	4.9 (1.7)	3.4 (1.7)	2.88^{+}	3.28*[b]
Activity level	4.3 (0.7)	4.3 (0.7)	4.1 (0.7)	0.43	0.41
Range of state	3.9 (0.8)	4.1 (0.8)	3.8 (1.0)	1.05	0.80
Peak of excitement	3.3 (1.1)	3.4 (1.0)	2.9 (1.0)	0.94	1.45
Rapidity of build-up	4.2 (1.5)	4.2 (1.6)	3.6 (1.4)	0.73	0.50
Irritability	4.3 (1.8)	4.86 (1.6)	5.0 (1.6)	1.83	0.66
Lability of states	3.3 (0.8)	3.9 (0.8)	3.5 (1.4)	0.96	0.80
Regulation of state	4.1 (1.1)	4.3 (1.2)	4.5 (1.6)	0.80	0.04
Cuddliness	4.7 (1.4)	5.1 (1.8)	4.5 (1.2)	1.70	1.70
Consolability	4.4 (1.5)	4.5 (1.2)	4.5 (2.2)	0.12	0.27
Self-quieting	3.9 (2.5)	4.0 (2.5)	4.5 (3.0)	0.29	0.06
Hand to mouth	3.5 (2.1)	3.6 (2.5)	3.8 (2.8)	0.17	0.03
Autonomic stability	5.8 (1.0)	6.1 (1.1)	6.0 (0.8)	2.28	1.42
Tremulousness	5.4 (1.8)	6.0 (2.1)	5.5 (1.4)	2.09	1.21
Startles	7.2 (1.3)	7.3 (1.5)	7.6 (1.0)	0.58	1.03
Lability of skin color	4.8 (1.2)	5.1 (1.3)	4.9 (1.0)	1.05	0.61
Reflex	2.4 (1.7)	2.5 (2.2)	3.2 (2.4)	0.93	0.29

$+ 0.05 < p < 0.1$, $* p < 0.05$.

[a] Smoker < Nonsmoker by HSD test.

[b] Smoker < Nonsmoker and Ex-smoker, respectively, by HSD test.

ANOVA was used to analyze the differences among the groups. The GLM was used to calculate adjustment for covariates. When differences were detected, the HSD test was used as a post-hoc test. Covariates were mother's education, the Raven score, the presence of smokers in family during pregnancy, sex, birth weight, the household income and the EES score.

Measurements of Neurobehavioral Development

Table 2 shows the means for the NBAS for the three groups. There were no significant differences among groups in the 7 clusters. Although it was not statistically significant, the children of smokers tended to have a lower score than the other two groups on 3 behavioral items; 'motor maturity' ($F_{(2, 282)} = 2.6$, $0.05 < p < 0.10$), 'pull to sit' ($F_{(2, 281)} = 2.9$, $0.05 < p < 0.10$) and 'defensive movements' ($F_{(2, 245)} = 2.9$, $0.05 < p < 0.10$). After adjusting the covariates, 2 behavioral items become statistically significant: 'pull to sit' ($F_{(2, 281)} = 3.6$, $p < 0.05$) and 'defensive movements' ($F_{(2, 245)} = 3.3$, $p < 0.05$).

Table 3 shows the means for the FTII and the BSID-II for the three groups. There were no statistically significant differences among the groups, even after adjustment for the covariates. Next, we examined the factors that could affect the FTII and the BSID-II. The EES and the household income were associated with the FTII and the BSID-II (Table 4). The EES was directly correlated with the MDI at 7 months (beta = 0.19, $p < 0.05$), and the PDI at 7 months (beta = 0.40, $p < 0.05$). Although it was not statistically significant, the EES score tended to correlate directly with the MDI at 18 months (beta = 0.32, $0.05 < p < 0.1$).

Table 3. Maternal smoking and the FTII, MDI, and PDI

	Nonsmoker	Ex-smoker	Smoker	F	
	M (SD)	M (SD)	M (SD)	Unadjusted	Adjusted
% of time looking at a novel target	59.2 (5.2)	59.2 (4.6)	58.4 (4.9)	0.12	0.30
MDI (7 months)	94.5 (5.9)	95.5 (6.0)	96.4 (5.4)	0.93	0.53
PDI (7 months)	89.0 (11.7)	89.0 (13.7)	94.3 (10.9)	0.93	0.95
MDI (18 months)	90.4 (11.2)	89.8 (9.9)	91.4 (12.6)	0.10	0.20
PDI (18 months)	84.6 (10.2)	82.7 (10.0)	80.6 (13.9)	1.26	0.88

n.s

% of time looking at a novel target, the score of the Fagan Test of Infant Intelligence (FTII); MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index. These MDI and PDI are indices of the Bayley Scales of Infant Development 2nd edition (BSID-II).

ANOVA was used to analyze the differences among the groups. The GLM was used to calculate adjustment for covariates. The covariates were the mother's education, the Raven score, the presence of smokers in the family during pregnancy, household income and the EES score.

Table 4. The EES, Household income, Raven score and FTII, MDI, and PDI

	7 months						18 months			
	% of time looking at a novel target		MDI		PDI		MDI		PDI	
	Beta (95%CI)	*F*	Beta (95%CI)	*F*	Beta (95%CI)	*F*	Beta (95%CI)	*F*	Beta (95%CI)	*F*
EES score	-0.11 (-0.28, 0.06)	1.67	0.19 (0.00, 0.38)	3.85 *	0.39 (0.01, 0.78)	4.08 *	0.37 (0.01, 0.73)	3.24^{+}	-0.24 (-0.57, 0.10)	1.91
Household income	-0.33 (-0.73, 0.06)	2.78^{+}	0.06 (-0.39, 0.51)	0.06	-0.72 (-0.16, 0.19)	2.41	0.56 -0.28, 1.41)	1.63	-0.34 (-1.13, 0.45)	0.72
Raven score	0.01 (-0.13, 0.15)	0.03	-0.02 (-0.18, 0.14)	0.06	-0.05 (-0.38, 0.28)	0.13	0.20 (-0.11, 0.50)	2.64	0.04 (-0.24, 0.33)	0.07

$+ 0.05 < p < 0.1$, $* p < 0.05$

% of time looking at a novel target, the score of the Fagan Test of Infant Intelligence (FTII); MDI, BSID-II Mental Developmental Index; PDI, BSID-II Psychomotor Developmental Index; EES, the Evaluation of Environmental Stimulation; the Raven score, the raw score of the Raven Standard Matrices.

The GLM was used to calculate adjustment for covariates. Covariates were the mother's education, smoking habit, the presence of smokers in the family postnatally and sex.

Discussion

Several early studies demonstrated the adverse effects of maternal smoking during pregnancy on motor function in the neonatal period. Law et al. (2003) examined the association of maternal smoking with infant neurobehavioral status 48 hours after birth. They found that infants of the smoking group showed more signs of stress and were hypertonic and excitable. Fried et al. (1987) [13] examined the association of infant neurological status with maternal cigarette smoking, marijuana use, and alcohol use. They assessed the neurological status using the Prechtl Neurological Examination at 9 and 30 days after birth, and found that maternal smoking during pregnancy was associated with hypertonicity and increased nervous system excitation, particularly at 30 days. Dempsey et al. (2000) [14] assessed neonatal neurobehavioral status with neurological examination, and found an association of neonatal hypertonicity with maternal smoking. In our previous report we found an association between maternal smoking during pregnancy and a lower score for muscle tone [23]. In the present study, we found significant associations between maternal smoking during pregnancy and lower scores for 'pull to sit' and 'defensive movements'. 'Pull to sit' evaluates muscle tone when the infant is pulled to sit, and 'defensive movements' evaluates the coordination of movement when a cloth is put on the infant's face. These 2 behavioral items, as well as muscle tone, are included in the motor cluster, and indicate muscle tone and motor coordination. Our findings appear to be in line with previous studies, and suggest that maternal smoking during pregnancy adversely affects neurobehavioral status, especially motor function, during the neonatal period.

However, there were no significant associations of maternal smoking during pregnancy with the results of the FTII and the BSID-II in children 7 and 18 months of age. Two possible explanations for this result should be considered. First, because of the interaction of postnatal environmental factors, the effects seen in the neonatal period become more difficult to observe. Indeed, several studies reported that the effects of maternal smoking during pregnancy virtually disappeared even after controlling for the quality of the home environment and the SES. Olds et al. (1994a) [34] examined the associations between maternal smoking during pregnancy and offspring neurobehavioral development during the first 4 years. After adjusting for covariates such as the quality of the home environment, the SES, and mother's IQ, maternal smoking was not associated with the BSID at 1 year of age or the Cattel scale at 2 years of age. Olds et al. (1994b) [35] pointed out the possibility that adequate quality of the home environment can offset the impairment in cognitive function associated with maternal smoking during pregnancy. Fried et al. (1988) [17] employed the BSID at 12 and 24 months of age, and examined the associations between maternal cigarette smoking, marijuana use and alcohol use. They found significant associations between maternal smoking and a lower MDI at 12 months of age and altered responses to auditory items at 12 and 24 months. However, at 24 months, the strong relationship of postnatal environmental factors with cognitive outcomes resulted in loss of the statistical significance of data. Trasti et al. (1999) [21] examined the association of maternal smoking in pregnancy with mental and motor development at age 1 and 5 years, respectively. No significant associations were found between maternal smoking and the BSID-II at 1 year of age. Children of smokers showed lower Whecsler Preschool and Primary Scale of Intelligence

Revised (WPPSI-R) scores at 5 years of age than children of nonsmokers. However, after controlling for maternal educational status, this difference was not statistically significant. Our findings may be in line with these studies. Furthermore, in the present study, positive associations were found between the EES and the BSID-II. The EES evaluates the quality of the home environment regarding child rearing. Although social class and economic status tend to have positive correlations to the home environment generally, no significant association was found between household income and the FTII and the BSID-II in the present study. Moreover, there was no statistically significant correlation between household income and the EES (data not shown). These findings suggest that the quality of the child-rearing environment has a great influence on child development, independent of the socioeconomic status. Additionally, the plausible adverse effects due to maternal smoking during pregnancy can be reduced by favorable environmental conditions such as compensatory postnatal caregiving. Another explanation for this result is that the effects of maternal smoking during pregnancy on development were unrelated to the domains of development measured by the FTII and the BSID-II. There is a possibility that the effects of maternal smoking could be detected in the NBAS, but not in the FTII and the BSID-II. To examine this possibility, correlations among the 3 developmental measurements were examined (Table 5). The 2 behavioral items of the NBAS, which were found to be significant in the analysis of maternal smoking, were not correlated with any of the indices in the FTII and the BSID-II. These results suggest that maternal smoking adversely affects neonatal neurobehavioral status; however, these effects could not be detected with the assessment tools we used in infancy.

Many studies have linked reductions of children's behavioral functions to maternal smoking during pregnancy [36][37][38][39]. Some of these studies indicated that the connection between maternal smoking and children's maladaptive behaviors was more consistent than the data about cognitive functions. One of the studies of the behavioral effects of maternal smoking during pregnancy assessed 1,377 pairs of twins 2 to 3 years of age using the Child Behavior Checklist (CBCL). Maternal smoking was associated with a significant increase in externalizing (e.g., oppositional, aggressive, overactive) but not internalizing (e.g., withdrawn, depressed, anxious) behavioral problems in both first and second born twins [37]. Wasserman et al. (1999) [38] replicated this finding in 191 children 4 to 5 years old, showing an association between maternal smoking and higher scores on all CBCL subscales except anxious/depressed and somatic complaints. These findings suggest that the effects of maternal smoking during pregnancy might appear in a child's behavioral domain with regard to attention, hyperactivity and maladaptive behavior.

Table 5. Correlations and partial correlations among the NBAS, FTII, and BSID-II

	7 months						18 months			
	% of time looking at a novel target		MDI		PDI		MDI		PDI	
	r	Partial r	r	Partial r	r	Partial r	r	Partial r	r	Partial r
Motor cluster	-0.02	-0.02	-0.04	-0.01	0.02	0.01	0.02	0.02	0.02	0.03
Pull to sit	-0.05	-0.08	-0.08	-0.06	-0.03	-0.01	-0.07	-0.03	-0.06	-0.06
Defensive movement	0.02	0.01	0.00	0.00	0.05	-0.00	0.07	-0.08	0.10	0.07

n.s

% of time looking at a novel target, the score of the Fagan Test of Infant Intelligence (FTII); MDI, BSID-II Mental Developmental Index; PDI, BSID-II Psychomotor Developmental Index; EES, the Evaluation of Environmental Stimulation; the Raven score, the raw score of the Raven Standard Matrices.

Spearman's r.

For calculating partial correlation, the Raven score, the EES score, and household income were used as covariates.

There are some limitations in this study. First, the data on maternal smoking habits were collected using a self-administered questionnaire. Objective measurements of salivary, serum, and urine cotinine levels were not perfomed. Although several studies found moderate correlations between self-reported smoking habits and biomarkers of cigarette exposure [40][41][42], misclassification of the maternal cigarette use cannot be ruled out. Second, compared with reports from the Japan Ministry of Health, Labour, and Welfare, in which the percentage of women who smoked during pregnancy was estimated to be 10.0% in 2000 [1], the percentage of smokers in the present study was low (3.4%). The small number of smokers may be a limitation of this study. As such, interpretation of the findings in the present study may require further consideration.

Finally, the present study reveals the adverse effects of maternal smoking during pregnancy on neurobehavioral status of offspring in their neonatal period. However, these effects were not observed on cognitive functions of offspring in their infancy. A significant association of the postnatal child rearing environment with child development was suggested. Several studies have indicated poorer behavioral function of offspring in their childhood due to maternal smoking during pregnancy. The present study is a prospective cohort study; evaluations of the long-term effects of maternal smoking during pregnancy on development of offspring from diverse viewpoints will be continued. The clinical significance of the negative change in motor function in the neonatal period is less well understood; it may have possible links to behavioral function in childhood. In the future we will readdress this health issue considering the interaction of the postnatal environmental factors with child development.

Conclusion

The present study examined the associations between maternal smoking during pregnancy and offspring development, considering the interaction of postnatal environmental factors. The results indicated that adverse effects of maternal smoking during pregnancy on neurobehavioral development of offspring could be detected in the neonatal period; however, these effects could not be found in their later infancy. The quality of the postnatal child-rearing environment was positively associated with the BSID-II, suggesting that the postnatal environment has a great influence on child development. Further studies examining the effects of maternal smoking on offspring development should take into consideration the roles of postnatal environmental factors in the interactions that determine child development.

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Relationship between child birth weight and concentration of polychlorinated biphenyls (PCBs) of the mother in Japan. –Tohoku Study of Child Development (TSCD)–

Naoyuki Kurokawa[1], Kunihiko Nakai[1], Keita Suzuki[1,2], Tomoyuki Nakamura[1,4], Kozue Sakurai[1], Miyuki Shimada[1], Takashi Ohba[1], Chieko Satoh[1], Satomi Kameo[1], Kunihiro Okamura[3], Hiroshi Satoh[1]

[1]Environmental Health Sciences, Graduate School of Medicine, [2]Department of Human Development and Disabilities, Graduate School of Education, [3]Department of Obestetrics, Graduate School of Medicine, Tohoku University, Sendai, Japan. [4]Miyagi Prefectural Institute of Public Health and Environment, Sendai, Japan.

Introduction

Birth weight is considered to be a predictor of a variety of adverse developments in childhood and beyond, including obesity, high blood pressure, cardiovascular disease and depression. There is widespread concern about potentially adverse health effects of environmental chemicals on children. Infants exposed *in utero* and during the early neonatal period are particularly vulnerable because of cell differentiation, the immaturity of metabolic pathways, and development of vital organ systems[1]. Exposure to persistent organochlorine compounds, including pesticides and industrial chemicals, is associated with detrimental effects on childhood neurobehavioral development. Studies in rhesus monkeys and rats showed that prenatal exposure to polychlorinated biphenyls (PCBs) was associated with reduced birth weight. In addition, certain unusual exposures such as those resulting from accidental poisoning by PCBs in Japan and Taiwan, have definitely been associated with low birth weight. Some studies also observed reduced birth weight and shorter gestation in infants with elevated PCB levels whose mothers consumed contaminated fish[2,3]. Thus, there is reason to believe that exposure to PCBs *in utero* may adversely affect the developing infant. The present study examines the association between exposure to PCBs *in utero* and infant birth weight.

Materials and Methods

We have been conducting a prospective cohort study, the Tohoku Study of Child Development (TSCD), to examine the effects of perinatal exposure to PCBs and methylmercury on neurobehavioral development in Japanese children. From January 2001 through September 2003 we recruited healthy pregnant women with their informed consent at obstetrics wards of two urban hospitals in the Tohoku region of Japan. Our cohort study is being conducted in a large city with a population of more than one million in order to assess the effect of the average exposure in pregnant Japanese women. The details of the study protocol were reported previously[4]. The TSCD was approved by the Medical Ethics Committee of the Tohoku University Graduate School of Medicine, and all mothers provided signed informed consent. In this analysis, the subjects were mother-infant pairs whose variables including the PCB concentration in cord blood, birth weight and other covariates were available. The infants were all singletons from full-term (37-42 weeks) gestation without congenital anomalies or diseases.

Birth weight in all infants was 2500g or more since low birth weight was used as an exclusion criterion. Information was obtained about pregnancy, delivery and infant characteristics from medical records. We obtained information about smoking status (nonsmoker/ex-smoker and current smoker) and alcohol drinking (yes/no) during pregnancy from a questionnaire. Umbilical cord blood was collected into a clean bottle immediately after birth. The samples were frozen at -80°C until analysis. All 209 PCB congeners were analyzed using HR-GC/HR-MS. The analytical procedure was described previously[5]. The total PCB concentration represented the sum of all the measured congeners, expressed as ng/g-fat. The total mercury concentration in cord blood was measured by cold vapor atomic absorption. In the statistical analysis, total PCBs and mercury concentrations, birth weight and maternal body mass index (BMI) before pregnancy were logarithmically transformed because of skewed distribution. Parametric methods were applied throughout. Multiple regression analyses were performed for adjustment of covariates. The potential confounders were considered and identified on the basis of previous studies[2,3,6-10]. They were the maternal age at delivery, maternal BMI before pregnancy, mercury concentration in cord blood, maternal alcohol drinking and smoking during pregnancy, parity, gestational age, and the sex and birth weight of the infant. The significance level was set at 5%.

Results and discussion

The number of mother-infant pairs was 438. The characteristics of the mothers and infants are shown in Table 1. The mean maternal age at delivery was 31.3 (SD 4.4, range 20-42) years. BMI before pregnancy ranged between 16.0 and 45.0 kg/m^2, with only 27 (6.1%) being over 25 kg/m^2, which is defined as overweight. The mean weight of all infants was 3100.5 (SD 319.7) g, the median was 3097.0 g, with a range between 2506 and 4176 g. The infants consisted of 225 boys and 213 girls. The mean total PCB concentration in cord blood was 54.0 ng/g-fat (SD 33.1) (median 47.2), and total maternal fish intake was 23.5 kg/year (SD 16.7) (median 20.5). Table 2 shows the results of multiple regression analyses. The BMI before pregnancy and gestational age were positively associated with birth weight. There was no significant difference statistically in birth weight between nonsmokers and smokers (including ex-smokers) during pregnancy. The total PCB and mercury concentration in cord blood were negatively associated with birth weight, whereas the total fish intake was positively associated with birth weight. Thus, the results suggested that prenatal PCB exposure adversely affected fetal growth.

Our study found a significant decrease in birth weight associated with the total PCB concentration in cord blood at delivery. Several studies have investigated the potential association between PCB exposure and birth weight[2,3,6,8-11]. However, one strength of our study is that we used the cord blood PCB concentrations as the indicator of intrauterine exposure, not approximations such as a food frequency questionnaire. Although we have found that PCBs and mercury may be associated with reduced birth weight, the underlying mechanisms remain unknown. In addition, levels of toxicants such as PCB and mercury, as well as nutritive factors, including n-3 PUFA, vary among different fish types. The Japanese diet relies heavily on rice, fish and vegetables. Indeed, the Japanese eat great amounts of many kinds of fish. Regarding fish consumption, there is a report that some polyunsaturated fatty acids ingested from fish, in particular docosapentaenoic acid (DPA), increase birth weight[7].

Another report showed that fish consumption was a major source of mercury exposure for pregnant women, and a relationship between elevated mercury levels and increased risk of very preterm delivery[12]. Although we have found that fish consumption is associated with an increase in birth weight, we have not yet considered the polyunsaturated fatty acids that may be confounders in this analysis. Polyunsaturated fatty acids are provided by seafood and may be beneficial for pregnancy and offspring. Since both polyunsaturated fatty acids and PCBs have the same origin and thus are likely to be correlated, fish and seafood consumption may confound the association between PCBs and birth weight. Further studies will require consideration of the potential risks of fish intake in the context of potential benefits. Since the TSCD study is a prospective cohort study, we will readdress these health issues when the children become older.

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Table 1. Characteristics of the study population in this analysis

Variables	Mean±SD	Range
Birth weight (g)	3100.5±319.7	2506-4176
Mother's age at delivery (years)	31.3±4.4	20-42
Fish consumption (g/year)	23460±16716	0-147278
Body mass index before pregnancy (kg/m^2)	21.0±2.85	16.0-45.0
Gestational age (weeks)	39.7±1.13	37.0-41.9
Total PCB concentration (ng/g-fat)	54.0±33.12	6.37-274.21
Total mercury concentration (ng/g)	11.4±6.24	1.77-43.90

Variables	Number of participants by categories	
Infant gender	Boys: n=225	Girls: n=213
Parity	First: n=233	Second or more: n=205
Smoking status during pregnancy	Nonsmoker: n=396	Smoker/ex-smoker: n=42
Alcohol drinking during pregnancy	No: n=349	Yes: n=88

Table 2. Multiple linear regression results for independent predictors of birth weight in this analysis

Variables	β	Standardized β	p value
Mother's age at delivery	0.001	0.062	0.207
Fish consumption (g/year)	0.011	0.110	0.016
Body mass index before pregnancy (kg/m^2)	0.170	0.199	<0.001
Gestational age (weeks)	0.030	0.330	<0.001
Total PCB concentration (ng/g-fat)	-0.024	-0.126	0.009
Total mercury concentration (ng/g)	-0.017	-0.089	0.051
Infant gender (Boys)	0.014	0.139	0.001
Parity (2nd or more)	0.012	0.058	0.244
Smoking status (nonsmoker)	0.006	0.033	0.461
Alcohol drinking (No)	-0.005	-0.036	0.411

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Determination of dioxins and polychlorinated biphenyls in breast milk, maternal blood and cord blood from residents of Tohoku, Japan

Tomoyuki Nakamura[a,b,*], *Kunihiko Nakai*[a], *Tohru Matsumura*[c], *Shigeru Suzuki*[b], *Yoshinori Saito*[b], *Hiroshi Satoh*[a]

[a]*Environmental Health Sciences, Tohoku University Graduate School of Medicine, 2-1 Seiryo, Aoba-ku, Sendai 980-8575, Japan*
[b]*Miyagi Prefectural Institute of Public Health and Environment, 4-7-2 Saiwaicho, Miyagino-ku, Sendai 983-0836, Japan*
[c]*Institute of Environmental Ecology, Environmental Risk Research Center, IDEA Consultants, Inc., 1334-5 Riemon, Ooigawa 421-0212, Japan*

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ABSTRACT

Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) are bioaccumulative chemicals that are considered to be toxic contaminants based on several epidemiological studies. To elucidate exposure levels of these chemicals in the present study, concentrations of PCDD/DFs, dioxin-like PCBs (DL-PCBs) and PCBs in breast milk, maternal blood and cord blood obtained from the same participants registered in a birth cohort study in Tohoku, Japan, were measured. Congener-specific analysis revealed several differences in minor congeners of these compounds among the three specimen types, although major congeners were detected in the specimens. The toxicity equivalence quantity concentrations (1998 WHO-TEF) and PCBs in breast milk, maternal blood and cord blood on the whole and on a lipid basis were in the order of breast milk > maternal blood > cord blood. Pearson's correlation coefficients of TEQs and total PCBs among the three specimens were high, with the correlation coefficient of TEQ between breast milk and maternal blood being the highest ($r=0.94$, $p<0.001$). On the other hand, the TEQ between breast milk and cord blood was the lowest ($r=0.79$, $p<0.001$). Pearson's correlation coefficient between the TEQ and PCBs in each specimen was also high ($r=0.82$–0.95, $p<0.001$). The associations of chemical concentrations with maternal age, parity, fish intake, BMI and the rate of body weight increase during pregnancy were analyzed with multiple linear regression analysis. TEQ concentrations and PCBs were negatively associated with parity ($p<0.05$), and maternal age was positively associated with PCBs ($p<0.05$). However, the associations with BMI and fish intake during pregnancy were not significant. These results suggest that parity is an important factor affecting the concentrations of dioxins and PCBs in these specimens.

1. Introduction

Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) are considered to be bioaccumulative chemical toxins that are resistant to degradation, and are detected in almost all human biological samples such as breast milk and blood in industrialized countries (Schecter et al., 2006). The main source of

* *Corresponding author*. Environmental Health Sciences, Tohoku University Graduate School of Medicine, 2-1 Seiryo, Aoba-ku, Sendai 980-8575, Japan. Tel.: +81 22 717 8103; fax: +81 22 717 8106.
E-mail address: nakamura@ehs.med.tohoku.ac.jp (T. Nakamura).

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