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Perinatal dioxin exposure and psychosocial and behavioral development in school-aged children

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ABSTRACT

Objective: The aim of this study was to elucidate the association between psychosocial and behavioral problems in children at school age and dioxin level in breast milk or estimated dioxin exposure (EDE) through breastfeeding in the general Japanese population.
Methods: Dioxin level of breast milk at 1 month of age and breastfeeding ratio through the first year of life were used to calculate the EDE of infants born in 1998–2005 in Japan. The Japanese Social Difficulties Questionnaire (SDQ) for the assessment of children's behavior was sent by mail to mothers whose breast milk underwent the dioxin survey, at the time when their infants were aged 6–13 years.
Results: The study subjects were 175 pairs of mothers and their first infants (79 boys, 96 girls). The mean total dioxin levels of breast milk were 18.3 and 19.8 (pgTEQ/g fat) and EDEs were 16.4 and 19.6 (ngTEQ/kg/year) in boys and girls, respectively. In linear multiple regression analyses after adjusting for age at SDQ, maternal age, birth weight and maternal smoking habit, dioxin level in breast milk was not significantly related to the total difficulties score (TDS) of SDQ in boys, B = 2.29 (95% CI −7.60–12.18), or in girls, B = −1.04 (95% CI −9.24–7.15). EDE correlated to the TDS in neither boys, B = −0.99 (95% CI −4.14–2.15), nor girls, B = 1.08 (95% CI −2.69–4.85).
Conclusion: No evidence was found of a correlation between perinatal dioxin exposure and behavioral and psychosocial problems of children measured by SDQ. These results support the benefits of recommending breastfeeding.

1. Introduction

Environmental contamination of organohalogen compounds, such as dioxins and polychlorinated biphenyls (PCBs), is of concern, especially exposure in utero and transfer through breastfeeding to infants. Because the developing brain is more vulnerable to these compounds than the adult brain, they could affect the neurodevelopment of infants and cause cognitive, psychological or psychiatric problems thereafter [1–3]. Most of the previous studies dealt with prenatal PCB and/or dioxin exposure, but few of them focused on postnatal intake through breastfeeding and the influence of perinatal exposure on neurodevelopment is unclear. In a dioxin-contaminated area in Southern Vietnam, Tai et al. reported that the levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)- and polychlorinated dibenzo-*p*-dioxin/furan (PCDD/PCDF)-toxic equivalents in breast milk and the estimated infant daily dioxin intake (DDI) via breastfeeding were inversely correlated to neurodevelopmental scores in 4-month-old infants [4]. The Duisburg Birth Cohort Study group showed that either maternal blood or milk levels of PCDD/PCDF and PCB at environmental background levels did not associate with the mental and motor developmental scores of the Bayley Scales of Infant Development of children at 24 months [5].

We previously reported on the dioxin levels of breast milk in the general population in Japan [6]. It would be of particular importance to investigate whether dioxin exposure at these background levels could affect the neurodevelopment and behavioral development of children in the long term [7]. The aim of this study was thus to elucidate whether the levels of prenatal and early postnatal dioxin exposure are associated with behavioral problems of school-aged children in our

Abbreviations: DDI, daily dioxin intake; EDE, estimated dioxin exposure; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzo-*p*-dioxins; PCDFs, polychlorinated dibenzofurans; TCDD, tetrachlorinated dibenzo-*p*-dioxins; TDI, tolerable daily intake; TDS, total difficulties score; TEQ, toxic equivalence; SDQ, Strengths and Difficulties Questionnaire.

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study population. We used dioxin concentration in breast milk itself as an indicator of prenatal exposure [5,8]. For early postnatal exposure, we calculated the estimated dioxin exposure (EDE) through breastfeeding using the dioxin levels and the ratio of breastfeeding throughout the first year of life [9]. The Strengths and Difficulties Questionnaire (SDQ), the Japanese parent version [10], was used to assess behavioral and psychosocial problems; it has been widely used to screen for child developmental disabilities, and psychological and psychiatric conditions or disorders [11].

2. Materials and methods

2.1. Human milk survey for dioxins

A human milk survey has been conducted in several prefectures and cities in Japan since 1997. The details of this survey carried out in various areas have been described in previous reports [6,12]. Healthy pregnant women aged between 20 and 39 years were recruited and signed informed consent was obtained from all of the participants. Approximately 30 ml of breast milk was collected manually from each participant at the time of a 1-month check-up for a baby. Polychlorinated dibenzo-*p*-dioxins (PCDDs, seven isomers), PCDFs (10 isomers) and coplanar PCBs (12 isomers), which are known as dioxin-like PCBs, were measured using gas chromatography and mass spectrometry, and were quantified by lipid-based calculations [6,12]. The levels of dioxins were described as the toxic equivalence (TEQ) values per gram of fat in breast milk by using toxic equivalent factors of 2,3,7,8-TCDD, which was previously documented in the 2005 World Health Organization (WHO) re-evaluated toxic equivalency [13]. The study protocol was approved by the medical ethics committee of Jichi Medical University, Tochigi, Japan, and all of the participating facilities.

2.2. Study subjects

In this study, the subjects were mother–child pairs in which birth occurred between 1998 and 2005. Because dioxin levels in breast milk are known to be decreased by a previous history of breastfeeding, primiparous mothers and their infants were analyzed in this study [14,15]. Information was collected using the first questionnaire at the time of consent from the mother, which included mother's age, weight, height and smoking habits, and using the second questionnaire at a 1-month check-up for the child, which included parity, gestational age, birth weight and gender. Breastfeeding status at each month until 12 months of age was obtained using the third questionnaire at a 1-year check-up for the children. In addition, blood samples were collected at 1 year of age from children born in 2003 to 2005 whose mothers' consent had been obtained. Concentrations of PCDDs and PCDF levels in the blood were measured by the same method used for the breast milk samples [6].

2.3. Estimation of dioxin exposure (EDE) through breastfeeding

The following equation was used to estimate the postnatal dioxin exposure by breastfeeding for the first year of life: EDE through breastfeeding, ng TEQ/kg/year = V {total volume of breast milk intake for the first year (ml/kg/year)} × L {% lipid content of breast milk/100 (g)} × Y {total dioxin levels (pg TEQ/g fat) × 10^{-3}} [9, 15]. We made the following assumptions for EDE. Firstly, the ratio of breastfeeding (R0–R11) was calculated monthly from 0 to 11 months according to the type of feeding recorded using the questionnaire, which was equal to 1 when feeding only on breast milk, 0.75 when breastfeeding exceeded formula feeding, 0.5 when breastfeeding and formula feeding were equal, 0.25 when formula feeding exceeded breastfeeding and 0 when feeding only on feeding formula. Secondly, average volume of daily milk intake and average body weight at 0 to 2 months, at 3 to 5 months, at 6 to 8 months and at 9 to 11 months by gender were obtained according to the Dietary Reference Intakes for Japanese 2010 [16]. The following formulas were used: V = [780 ml × (R0 + R1 + R2)/4.9(kg) + 780 ml × (R3 + R4 + R5)/7.4(kg) + 600 ml × (R6 + R7 + R8)/8.5(kg) + 450 ml × (R9 + R10 + R11)/9.1(kg)] × 365/12 in boys and V = [780 ml × (R0 + R1 + R2)/4.6(kg) + 780 ml × (R3 + R4 + R5)/6.8(kg) + 600 ml × (R6 + R7 + R8)/7.8(kg) + 450 ml × (R9 + R10 + R11)/8.5(kg)] × 365/12 in girls. Thirdly, because the lipid concentration in breast milk varies individually and over the period of lactation, we used the mean lipid contents in the breast milk of the study subjects in the calculation. The average daily dioxin intake (DDI, pg TEQ/kg/day) for the first year was calculated as follows: (EDE through breastfeeding × 10^3)/365.

2.4. SDQ score measurement

Japanese forms of SDQ were sent via mail to parents of the subjects whose mothers' milk underwent dioxin survey [10]. Children of the subjects were aged between 6 and 13 years at evaluation. Parents were asked to complete the extended Japanese version of SDQ, which comprised 25 items on specific strengths and difficulties, with an overall rating of whether their child had behavioral or psychological problems. The four SDQ subscales (emotional symptoms, conduct problems, hyperactive/inattention and peer problems) representing problem scores were obtained and the total difficulties score (TDS) rating of 0 to 40 was obtained, by adding the 4 subscale scores according to the instructions of SDQ [11]. Another subscale of prosocial behavior assesses the positive aspects of child behavior.

2.5. Statistical analyses

Because a gender difference has been reported in the milk intake volume during the first year of life [16], and gender and age effects have been shown in the Japanese version of SDQ [10,17], the study subjects were stratified into subgroups by gender and by age (6–10 years, 11–13 years). We employed non-parametric methods for analyses since the dioxin level in breast milk and EDE were not distributed normally. Spearman's rank correlations were used to explore the association between total dioxin level in breast milk or EDE by breastfeeding and the five subscale scores of SDQ.

Linear multiple regression analyses were performed to examine the association between TDS and the total dioxin level in breast milk or EDE through breastfeeding after $\log_{10}$ transformation. Adjustment for covariates, including maternal age, birth weight, any history of maternal cigarette smoking and age at SDQ assessment in boys and in girls, was performed. These covariates were chosen from the questionnaires as they have been reported to be related to the TDS of SDQ or the behavior of children [10,11,17]. In addition, to verify the correlation between dioxin exposure and the TDS of SDQ, the medians of TDS were compared between the children with high EDE in the top 10 percentiles and those with low EDE in the bottom 10 percentiles in boys and in girls. Results were considered significant at $p < 0.05$. All analyses were performed with SPSS 19.0 (IBM Japan, Tokyo, Japan).

3. Results

The study subjects consisted of 175 pairs of primiparous mothers and their children who replied and completed the 25 SDQ items in the 316 pairs to whom SDQ was sent. The residences of the study subjects extended across 20 prefectures in Japan. They were neither high- nor low-risk areas for dioxin pollution. The characteristics of the mother and child (79 boys and 96 girls) pairs and breastfeeding status are shown in Table 1. As represented by the breastfeeding ratios, breastfeeding was dominant until 8 months and equal to

Table 1
Characteristics of the mother and infant pairs and breastfeeding status by gender.

	Boys	Girls
	n = 79	n = 96
Mothers		
Age (years), mean ± SD	29.8 ± 2.5	29.5 ± 2.7
Weight (kg), mean ± SD	50.6 ± 6.3	51.5 ± 6.2
Height (cm), mean ± SD	156.8 ± 5.4	158.0 ± 5.3
Any history of smoking habit, n(%)	17(22)	22(23)
Smoking habit during pregnancy, n(%)	0(0.0)	2(2.1)
Infants		
Gestational age (weeks), mean ± SD	39.6 ± 1.2	39.9 ± 1.3
Birth weight (g), mean ± SD	3067 ± 340	3001 ± 348
Birth length (cm), mean ± SD	49.3 ± 2.0	49.0 ± 1.7
Birth head circumference (cm), mean ± SD	33.1 ± 1.5	32.8 ± 1.2
Breastfeeding ratio		
0–2 months, mean ± SD	0.73 ± 0.27	0.81 ± 0.24
3–5 months, mean ± SD	0.61 ± 0.41	0.69 ± 0.39
6–8 months, mean ± SD	0.52 ± 0.46	0.59 ± 0.44
9–11 months, mean ± SD	0.43 ± 0.46	0.43 ± 0.45
Age of infants at SDQ		
6–10 years, n(%)	31(39)	40(42)
11–13 years, n(%)	48(61)	56(58)

SDQ: Social Difficulties Questionnaire, SD: standard deviation.
Breastfeeding ratio: 1 when feeding only on breast milk, 0.75 when breastfeeding exceeded formula feeding, 0.5 when breastfeeding and formula feeding were equal, 0.25 when formula feeding exceeded breastfeeding and 0 when feeding only on feeding formula.

formula feeding thereafter in both gender groups. At the time of SDQ assessment, 48 (61%) boys and 56 (58%) girls were 11 to 13 years old.

Means, medians and interquartile range of dioxin concentrations measured in the breast milk at 1 month are presented in Table 2. There were no significant differences in the levels of PCDDs, PCDFs, dioxin-like PCBs and total dioxin level in the milk between the groups of boys and girls. The mean dioxin exposure through breastfeeding was estimated to be 16.4 ng TEQ/kg/year for boys and 19.6 ng TEQ/kg/year for girls. From these EDE levels, the mean DDI for the first year of life was calculated at 44.9 pg TEQ/kg/day in boys and 53.7 pg TEQ/kg/day in girls. The blood dioxin levels were measured in eight children at 1 year to evaluate whether our estimation was relevant. The EDE was highly associated with the blood dioxin levels in these children (Supplemental Fig. 1, Spearman's $\rho = 0.905$, $p = 0.002$).

The means of TDS of SDQ were 8.7 in boys and 7.4 in girls. Although the means of TDS and three problem subscale scores were higher in boys than in girls, a significant difference was found only in hyperactive/inattention score (Supplemental Table 1). The prosocial behavior score, which is a positive behavior subscale, was higher in girls than in boys, but the difference was also not significant. Comparing the groups aged 6–10 and 11–13, the means of TDS and subscales of conduct problem and hyperactive/inattention scores were significantly higher in the group aged 6–10.

There was no significant association between TDS of SDQ and total dioxin level in boys: Spearman's $\rho = -0.22$, $p = 0.05$, or in the group aged 6–10: Spearman's $\rho = -0.12$, $p = 0.33$, and aged 11–13: Spearman's $\rho = -0.16$, $p = 0.11$. A weak negative correlation was found in girls, with Spearman's $\rho = -0.24$, $p = 0.02$. Among the five subscales of SDQ, conduct problem scores and hyperactive/inattention scores were negatively correlated, meaning that a higher dioxin level in breast milk was related to fewer behavioral problems in girls. There was no significant association between other subscales and total dioxin level (Supplemental Table 2).

No significant association was found between TDS and EDE through breastfeeding in boys: Spearman's $\rho = -0.18$, $p = 0.11$, or in girls: Spearman's $\rho = -0.03$, $p = 0.79$, or in the groups aged 6–10: Spearman's $\rho = -0.20$, $p = 0.11$, and aged 11–13: Spearman's $\rho = -0.08$, $p = 0.45$. In addition, no correlation between any subscales of SDQ and EDE through breastfeeding was found in boys and in girls. A weak negative correlation was found between conduct problem scores and EDE in the group aged 6–10, with Spearman's $\rho = -0.26$, $p = 0.03$ (Supplemental Table 3).

In linear multiple regression models to examine the association between total dioxin level in breast milk and TDS of SDQ, total dioxins did not affect the TDS significantly in boys, B = 2.29 (95% CI −7.60–12.18, $p = 0.46$), or in girls, B = −1.04 (95% CI −9.24–7.15, $p = 0.80$). Younger age at SDQ assessment both in boys and girls and any history of maternal cigarette smoking only in boys increased TDS (Table 3). Similar results were obtained in the models in which EDE through breastfeeding instead of the dioxin level was included. The EDE was not a significant factor for the TDS of SDQ either in boys, B = −0.99 (95% CI −4.14– 2.15, $p = 0.53$), or girls, B = 1.08 (95% CI −2.69–4.85, $p = 0.57$) (Table 4). The medians (interquartile range) of TDS of SDQ of the children with high EDE in the top 10 percentiles were 5 (3–10) in boys and 5 (3–15) in girls, while those of the children with low EDE in the bottom 10 percentiles were 8 (6–12) in boys and 7 (6–12) in girls. There were no significant differences between the medians of TDS or subscale scores between the high-EDE group and the low-EDE group in either boys or girls (Supplemental Table 4).

4. Discussion

To the best of our knowledge, the present study provides the first evidence that either estimated prenatal or lactational dioxin exposure did not correlate with behavior assessed using the Japanese parent-rated SDQ of children living in Japan. Dioxin concentration in the breast

Table 2
Dioxin level in the breast milk at 1 month and estimated dioxin exposure through breastfeeding.

	Boys (n = 79)		Girls (n = 96)	
	Mean (SD)	Median (interquartile range)	Mean (SD)	Median (interquartile range)
Dioxin level in breast milk				
PCDDs (pg TEQ/g fat)	8.6 (3.1)	8.3 (6.6–10.3)	9.2 (3.7)	8.6 (6.3–11.3)
PCDFs (pg TEQ/g fat)	3.2 (1.5)	3.0 (2.4–3.6)	3.4 (1.4)	3.1 (2.4–4.2)
Co PCBs (pg TEQ/g fat)	6.5 (2.5)	6.2 (4.7–7.9)	7.2 (2.8)	6.6 (5.3–9.3)
Total dioxins (pg TEQ/g fat)	18.3 (6.2)	17.8 (13.9–21.7)	19.8 (7.1)	18.6 (14.0–25.3)
Fat in breast milk (g/100 ml)	4.1 (1.4)	4.1 (3.1–5.1)	3.9 (1.3)	3.8 (3.0–4.7)
Total volume of breast milk intake (ml/kg/year)	21716 (11499)	22691 (10894–33886)	25895 (11734)	30511 (15078–36747)
EDE (ng TEQ/kg/year)	16.4 (10.7)	14.0 (8.0–23.0)	19.6 (10.8)	18.8 (11.4–26.3)
DDI (pg TEQ/kg/day)	44.9 (29.3)	38.5 (22.0–62.9)	53.7 (29.6)	51.4 (31.2–72.0)

PCDDs: polychlorinated dibenzo-p-dioxins (sum of 2,3,7,8-tetra CDD, 1,2,3,7,8-penta CDD, 1,2,3,4,7,8-hexa CDD, 1,2,3,6,7,8-hexa CDD, 1,2,3,7,8,9-hexa CDD, 1,2,3,4,6,7,8-hepta CDD and octa CDD).
PCDFs: polychlorinated dibenzofurans (sum of 2,3,7,8-tetra CDF, 1,2,3,7,8-penta CDF, 2,3,4,7,8-penta CDF, 1,2,3,4,7,8-hexa CDF, 1,2,3,6,7,8-hexa CDF, 1,2,3,7,8,9-hexa CDF, 2,3,4,6,7,8-hexa CDF, 1,2,3,4,6,7,8-hepta CDF, 1,2,3,4,7,8,9-hepta CDF, octa CDF).
Co PCBs: coplanar polychlorinated biphenyls (sum of PCB 77, 81, 126, 169, 105, 114, 118, 123', 156, 157, 167 and 189).
TEQ: toxic equivalence by the World Health Organization in 2005, EDE: estimated dioxin exposure.

Table 3
Linear multiple regression analysis to examine association between total dioxin level in breast milk and TDS of SDQ.

	Boys				Girls			
	B	(95% CI)	beta	p	B	(95% CI)	beta	p
Log_{10} (total dioxins)	2.29	(−7.60 – 12.18)	0.06	0.46	−1.04	(−9.24 – 7.15)	−0.03	0.80
Age at SDQ	−0.69	(−1.27 – −0.12)	−0.30	0.02	−0.43	(−0.91 – 0.05)	−0.20	0.08
Maternal age	−0.36	(−0.83 – 0.11)	−0.16	0.13	0.31	(−0.11 – 0.74)	0.15	0.15
Birth weight	−0.002	(−0.006 – 0.001)	−0.14	0.21	−0.001	(−0.004 – 0.003)	−0.04	0.73
Any history of smoking habit	3.28	(0.26 – 6.30)	0.24	0.03	0.68	(−2.08 – 3.44)	0.05	0.63

B: partial regression coefficient.
beta: standardized partial regression coefficient.
TDS: total difficulties score.

milk at 1 month after delivery was considered as an indicator of prenatal exposure and lactational exposure was estimated according to the dioxin levels of breast milk and the ratio of breastfeeding to formula feeding during the first year.

The average DDI of the infants during the first year of life calculated from the EDE in this study was 10 to 14 times higher than the tolerable daily intake (TDI) (i.e. 4 pg TEQ/kg/day) for the general population, as defined by the WHO or by the Japanese Ministry of Health, Labour and Welfare [13,18]. This result is compatible with previous reports stating that DDI in breastfed infants is 4 to 40 times higher than the TDI because of the high transfer via the mother's milk [14,15]. The EDE level in our study was similar or slightly higher than the estimated dioxin exposure levels in infants by breastfeeding recently reported in Japan and other countries [14,19–21]. Dioxin level in breast milk is known to decrease after several months, reflecting a decrease in the burden on the mother by breastfeeding [15]. However, this decrease may not be linear during the lactation period and may differ from mother to mother [15,21]. We did not, therefore, take the decrease in months into consideration and the EDE level in this study might have been overestimated. On the other hand, actual PCDD level in breast milk at 1 month was comparable to the levels in other studies [14,19–21]. Thus, we analyzed the associations of both dioxin level in breast milk and EDE level to TDS of SDQ. No linear dose–effect association between either dioxin level itself or EDE and TDS was observed, meaning that an increase of dioxin intake from breast milk was not associated with behavioral problems of children. We found no significant differences in the TDS or subscale scores of SDQ between the cases with a high EDE level and those with a low EDE level. These results suggested that the perinatal dioxin exposure in the range in this study population did not affect the behavioral and psychosocial development of the children.

SDQ is a screening instrument to assess positive and negative aspects of children's behavior; it can be filled in by parents or teachers, and was originally published in English [11]. The Japanese parent-rated SDQ was validated by Matsuishi et al. and normative data of Japanese school-aged children were reported very recently [10,17]. The means of TDS and four subscale scores relating to problematic behavior in this study were similar to the validation study and slightly higher than the scores reporting normative data [17]. However, the distribution patterns of the four subscale scores and the effects of gender and age on the scores, namely, higher hyperactivity/inattention scores or TDS for boys than for girls, and TDS and scores for emotional symptoms and hyperactivity/inattention tending to be lower in older children, were similar to those in these studies and studies in other countries [10,17, 22]. Thus, we could assume that the scores of the parent-rated SDQ obtained in this study were reasonable.

It has been revealed that perinatal dioxin exposure may affect neurobehavioral development; however, the identified effects appear to be contradictory and subtle [1–3,5,23]. In animal models, exposure *in utero* and via lactation to a low dose of TCDD disrupted the functions of memory and emotion in male mouse offspring [24]. The pups reaching adulthood showed behavioral inflexibility, compulsive repetitive behavior and lowered competitive dominance [25]. Maternal TCDD exposure delayed motor development assessed by righting response from an inclined position of the offspring at an early stage, especially in male rats [26]. The effects on learning behaviors are, however, controversial; TCDD-exposed rats made more errors in the early phase of the learning process in terms of spatial discrimination/reversal learning, but they improved in terms of performance in the visual discrimination/reversal learning task compared with the control group [27].

In human studies, because environmental exposure levels are much lower than those in animal models, the effect of perinatal exposure on neurodevelopment and behavior in children remains unclear. Although it is difficult to distinguish the effect between prenatal and postnatal exposure, more significant correlations were found for prenatal exposure, especially that to PCBs. In children from Michigan and North Carolina whose mothers had consumed fish presumed to be contaminated with PCBs, levels of prenatal PCB exposure were associated with adverse outcomes such as greater impulsivity, poorer concentration and poorer working memory only in children who had not been breastfed [28]. Sioen et al. studied prenatal exposure to environmental contaminants of lead, cadmium, PCBs and dioxin-like compounds measured in cord blood and behavioral problems at 7–8 years using SDQ [29]. Although higher lead exposure was associated with a higher risk for hyperactivity in both boys and girls, higher prenatal exposure to dioxin-like compounds was found to be associated with a lower score for hyperactivity. Recently, the Duisburg Birth Cohort Study showed similar results; PCDD/PCDF and PCB in maternal blood negatively associated with hyperactive behavior of school-aged children, while the effect of the amount of PCDD/PCDF and PCB ingested with breast milk was not

Table 4
Linear multiple regression analysis to examine association between EDE through breastfeeding and TDS of SDQ.

	Boys				Girls			
	B	(95% C.I.)	beta	p	B	(95% C.I.)	beta	p
Log_{10} EDE	−0.99	(−4.14 – 2.15)	−0.07	0.53	1.08	(−2.69 – 4.85)	0.06	0.57
Age at SDQ	−0.61	(−1.11 – −0.11)	−0.27	0.02	−0.47	(−0.91 – −0.03)	−0.22	0.04
Maternal age	−0.34	(−0.81 – 0.12)	−0.16	0.15	0.31	(−0.11 – 0.73)	0.15	0.15
Birth weight	−0.002	(−0.005 – 0.002)	−0.12	0.29	0.000	(−0.004 – 0.003)	−0.03	0.78
Any history of smoking habit	3.10	(0.21 – 5.99)	0.23	0.04	0.92	(−1.80 – 3.64)	0.07	0.50

B: partial regression coefficient.
beta: standardized partial regression coefficient.
EDE: estimated dioxin exposure, TDS: total difficulties score.

significant [30]. In contrast to the assumed unfavorable effects of dioxins and dioxin-like compounds on neurological or developmental measurements, we have to consider that a number of benefits of breastfeeding for short- and long-term health as well as optimal brain development in children have been noted [31].

One of the limitations of this study is the potential bias due to a lack of SDQ data via mailing questionnaires, and 55% of the mailed subjects completed SDQ. The mothers who responded to SDQ questionnaires could be more conscious of the subject matter or have concerns over their children's behavior, as shown by the slightly higher TDS in our study than the Japanese normative data [17]. However, the dioxin level in breast milk and EDE in the subjects ranged widely and linear multiple regression analysis was performed, which supported the absence of a significant correlation between dioxin exposure and the behavior of the children. Because SDQ is a tool for screening children's psychological and psychiatric conditions, to clarify the influence on psychological and psychiatric development of children in the longer term, longitudinal follow-up and diagnostic evaluations are needed. The second limitation is that we could not include socio-demographic covariates, for example, education level of the parents, maternal alcohol consumption and economic status, which are known as cofounders for children's behavior [29,30]. Only maternal age and maternal smoking habit were available from the questionnaires and were included in the analyses. In addition, simultaneous exposure to other environmental contaminants like heavy metals, such as lead, cadmium, mercury, or pesticides, which may affect neurodevelopmental disorders in children, was not measured in this study [29,32].

In summary, we investigated the correlation between dioxin level in breast milk, dioxin exposure via breastfeeding and behavioral and psychosocial problems using SDQ in pairs of mothers and children in the general Japanese population. There was no significant association between TDS of SDQ and dioxin level in breast milk or EDE. This supports the benefits of breastfeeding and provides evidence that breastfeeding should be recommended, even in the presence of measureable amounts of dioxins in the current environment.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.earlhumdev.2015.06.001.

Conflict of interest statement

None.

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Outcomes of Infants Born at 22 and 23 Weeks' Gestation

WHAT'S KNOWN ON THIS SUBJECT: The remarkable improvement in the survival of extremely premature infants has been well documented. However, there have been few cohort studies large enough to determine the neurodevelopmental outcomes of survivors born at 22 or 23 weeks.

WHAT THIS STUDY ADDS: The proportions of unimpaired or minimally impaired were 12.0% at 22 weeks (n = 75) and 20.0% at 23 weeks (n = 245). The outcomes were inferior compared with those for infants born at 24 and 25 weeks, but were improved compared with those in previous studies.

abstract

OBJECTIVE: To provide instructive information on death and neurodevelopmental outcomes of infants born at 22 and 23 weeks' gestational age.

METHODS: The study cohort consisted of 1057 infants born at 22 to 25 weeks in the Neonatal Research Network, Japan. Neurodevelopmental impairment (NDI) at 36 to 42 months' chronological age was defined as any of the following: cerebral palsy, hearing impairment, visual impairment, and a developmental quotient <70. A systematic review was performed by using databases of publications of cohort studies with neonatal and neurodevelopmental outcomes at 22 and 23 weeks.

RESULTS: Numbers and incidences (%) of infants with death or NDI were 60 (80%) at 22 weeks and 156 (64%) at 23 weeks. In logistic regression analysis, gestational ages of 22 weeks (odds ratio [OR]: 5.40; 95% confidence interval [CI]: 2.48–11.76) and 23 weeks (OR: 2.14; 95% CI: 1.38–3.32) were associated with increased risk of death or NDI compared with 24 weeks, but a gestational age of 25 weeks (OR: 0.65; 95% CI: 0.45–0.95) was associated with decreased risk of death or NDI. In the systematic review, the medians (range) of the incidence of death or NDI in 8 cohorts were 99% (90%–100%) at 22 weeks and 98% (67%–100%) at 23 weeks.

CONCLUSIONS: Infants born at 22 and 23 weeks' gestation were at higher risk of death or NDI than infants at born at 24 weeks. However, outcomes were improved compared with those in previous studies. There is a need for additional discussions on interventions for infants born at 22 or 23 weeks' gestation. *Pediatrics* 2013;132:62–71

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KEY WORDS

extremely preterm infants, neurodevelopmental, outcome of high-risk infants, cerebral palsy, cognitive impairment

ABBREVIATIONS

CI—confidence interval
CLD—chronic lung disease
CP—cerebral palsy
DQ—developmental quotient
GMFCS—Gross Motor Function Classification System
IVH—intraventricular hemorrhage
KSPD—Kyoto Scale of Psychological Development
NDI—neurodevelopmental impairment
OR—odds ratio
ROP—retinopathy of prematurity

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The remarkable improvement in the survival of extremely low birth weight infants has been well documented.[1,2] Increased extremely low birth weight infant survival rates have paralleled improvements in prenatal and neonatal care.[3] The outcomes after 24 weeks' gestational age have been well estimated and evaluated.[4–21]

There recently have been several notable reports on 22 and 23 weeks' gestational age; the short-term outcomes of these extremely premature infants seem to have improved, but the long-term outcomes are still unfavorable.[6–18] Decisions to initiate or withhold intensive care for these extremely premature infants are highly controversial, in contrast to those for infants born at 24 and 25 weeks' gestational age.[22–24] Physicians and parents contemplating the prognosis of extremely preterm infants require reliable information based on gestational age with which to plan care around the time of birth and thereafter.[4,25]

The aim of this study was to provide instructive information on death and neurodevelopmental outcomes of infants born at 22 and 23 weeks' gestational age and to compare them with those of infants born at 24 or 25 weeks from a large multicenter cohort and a systematic review.

METHODS

Study Subjects and Definitions

A total of 48 tertiary centers participated in a multicenter follow-up study of the Neonatal Research Network, Japan, in infants born at 22 to 25 weeks between January 1, 2003, and December 31, 2005.[5,6,26,27] Each center registered all very low birth weight infants who were admitted to the NICU within 28 days after birth, including infants transferred to the centers after birth (outborn). The infants who were born alive but died in the delivery room in the centers were registered. Infants who were recognized as born before 22 weeks 0 day were excluded.[6]

Demographic, perinatal, and infant data were collected from each center by using previously described definitions.[5,6,26,27] Gestational age was determined in the following order: obstetric history based on last menstrual period, with confirmation or correction by obstetric examination by using ultrasonography at the health checkup for pregnant women during the first trimester, and postnatal physical examinations of neonates. Premature rupture of membranes was defined as rupture of membranes before the onset of labor. Antenatal steroid use was defined as administration of any corticosteroid to accelerate fetal lung maturity. Maternal transport meant only emergency transport. Respiratory distress syndrome was diagnosed by using clinical and radiographic findings. Chronic lung disease (CLD) was defined as the use of supplemental oxygen on the 28th day after birth, and 36-week CLD was defined when an infant received supplemental oxygen at the postmenstrual age of 36 weeks. Symptomatic patent ductus arteriosus was diagnosed on the basis of both echocardiographic findings and clinical evidence of volume overload because of left-to-right shunt. Intraventricular hemorrhage (IVH) was reported according to the classification of Papile et al.[28] Cystic periventricular leukomalacia was diagnosed by cranial ultrasound or head MRI scans. Sepsis was defined as culture-proven septicemia or bacteremia at any time during the NICU stay. Necrotizing enterocolitis was defined according to the classification of Bell et al[29] as stage II or higher. The treatment of retinopathy of prematurity (ROP) was laser coagulation, cryocoagulation therapy, or both.

Neurodevelopmental Assessments

A comprehensive neurodevelopmental assessment was performed on the surviving infants at 36 to 42 months' chronological age. The assessment consisted of neurologic assessment, functional classification of hearing and visual ability, developmental evaluation, growth assessment, medical and social history, and interviews at each participating center.

The neuromotor examinations were performed by a trained pediatrician, not necessarily blinded to the perinatal details. Cerebral palsy (CP) was defined as a nonprogressive, nontransient central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture.[30] Profound CP was defined as a Gross Motor Function Classification System (GMFCS) level of 4 or 5.[31] Children with an unknown CP level were classified as having profound impairment. Children with any type of CP who were defined as GMFCS level 1 were excluded from the CP group and were included in the minimally impaired group.[13] Hearing impairment was defined as when amplification was required. Visual impairment was defined as blindness with no functional vision in 1 or both eyes.

The assessment of cognitive function was performed by using the Kyoto Scale of Psychological Development (KSPD) test.[32] This test was administered by experienced testers who were certified psychologists blinded to the perinatal details at each center. The developmental quotient (DQ) was derived by dividing developmental age by chronological age. A DQ score of 100.6 ± 13.4 represents the mean ± 1 SD at the time of standarization.[32] A DQ score <70 was interpreted as representing significantly delayed performance. If the KSPD assessment was not available, the pediatrician estimated the child's development level as delayed or not delayed. In cases judged as delayed, the developmental level was assumed as equivalent to a DQ score <50 in this study.

Neurodevelopmental impairment (NDI) was defined as any of the following: CP with a GMFCS level 2 to 5, hearing impairment, visual impairment, or a DQ score <70. Profound NDI was defined as profound CP and/or a DQ score <50.

Statistical Analyses

Characteristics by gestational age are described as means and SDs for continuous variables and as numbers and proportions for binary and categorical variables. Logistic regression was used to evaluate the relationship between risk factors and death or NDI at 3 years of age. We calculated odds ratios (ORs) and their 95% confidence intervals (CIs) by logistic regression using a reference of infants born at 24 weeks' gestational age. The selected biological and perinatal characteristics were gender, multiple birth, premature rupture of membranes, antenatal steroid use, maternal transport, being outborn, use of cesarean delivery, and gestational age because these were identified as variables associated with outcomes in previous follow-up studies.[7,33–38]

Systematic Review of Studies With Neonatal Outcomes at 22 and 23 Weeks' Gestation

The PubMed and Cochrane Library databases were searched by using a combination of the following words: extremely premature, infant, neurodevelopment, and outcome. The language was restricted to English. All potentially relevant titles and abstracts were retrieved and assessed for eligibility. The reference lists of relevant articles were reviewed, and relevant citations were retrieved if they had not been obtained in the primary search. Publications were selected for inclusion if they contained the following: (1) a publication date between January 1, 2000, and June 30, 2012; (2) outcomes of infants born during or after 1990; (3) the numbers of cases of death and NDI at 18 to 42 months for infants born at <28 weeks' gestational age; and (4) the numbers of evaluated infants at 18 to 42 months. For each eligible study, all reported components of death, NDI, and follow-up rates were extracted. The latest reports were chosen from the same cohorts or the same area.

RESULTS

During the study period, 1057 infants born at <26 weeks were registered with the Neonatal Research Network (Fig 1). Of these, 266 died in the NICU (25.2%), including 1 case not admitted to the NICU, and 791 (74.8%) survived to discharge. Nine infants died after discharge. Between January 2006 and December 2008, 562 of the 782 survivors visited a site for standardized follow-up assessment.

Demographic and perinatal characteristics, neonatal morbidities, and interventions were not different between infants evaluated and not evaluated, except that evaluated infants were more likely to require treatment of ROP (234 [41.7%] of evaluated infants, 73 [33.2%] of infants who were not evaluated), and were less likely to be outborn (47 [8.9%] of evaluated infants, 29 [13.2%] of infants who were not evaluated), experience neonatal seizure (30 [5.3%] of evaluated infants, 25 [11.4%] of infants who were not evaluated), and have grade 3–4 IVH (48 [8.6%] of evaluated infants, 30 [13.6%] of infants who were not evaluated).

As shown in Table 1, stratifying demographic and perinatal characteristics according to gestational weeks, infants with a birth weight <400 g were particularly common at 22 weeks. The use of antenatal steroids, maternal transport, being outborn, and cesarean delivery increased with increasing gestational weeks. Among neonatal morbidities, proportions of respiratory distress syndrome, neonatal seizure, IVH grades 3–4, and sepsis tended to decrease with increasing gestational weeks. Proportions of CLD at 36 weeks' corrected gestational age, ligation for patent ductus arteriosus, cystic periventricular leukomalacia, necrotizing enterocolitis, and ROP requiring any treatment were low in infants born at 22 weeks.

Table 2 shows neurodevelopmental outcomes grouped by gestational weeks of the evaluated infants. Seventy-five (13.7%) infants had CP,

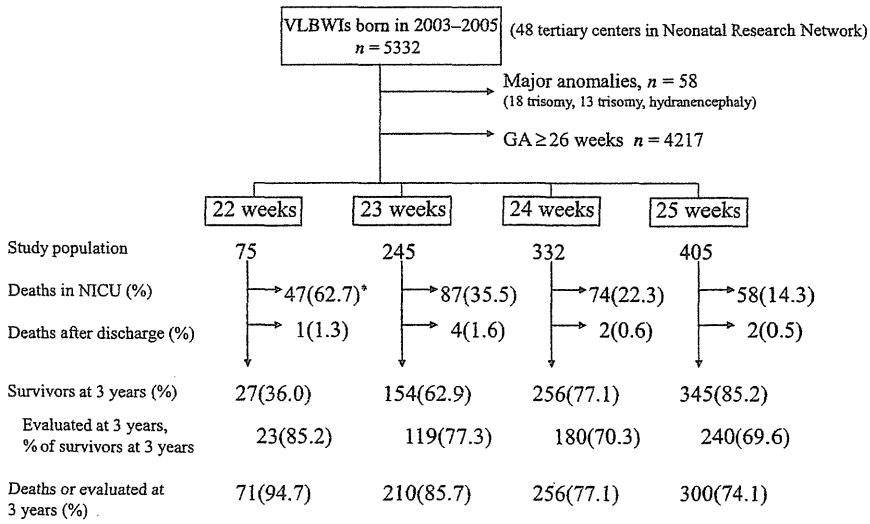

FIGURE 1
Study subjects by gestational age groups. *Includes 1 case born alive but not admitted to the NICU. GA, gestational age; VLBWI, very low birth weight infants.

TABLE 1 Characteristics of Study Cohort

	Gestational Age				
	22 Weeks (n = 75)	23 Weeks (n = 245)	24 Weeks (n = 332)	25 Weeks (n = 405)	Total N =1057
Demographic and perinatal characteristics					
BW, mean ± SD, g	488 ± 72	575 ± 80	634 ± 103	741 ± 137	651 ± 137
BW <400 g, *n/N* (%)	7/75 (9.3)	3/245(1.2)	7/332(2.1)	9/405(2.2)	26/1057 (2.5)
Male, *n/N* (%)	32/75 (42.7)	133/244[a] (54.5)	163/332 (49.1)	219/403[a] (54.3)	547/1054[a] (51.9)
Multiple birth, *n/N* (%)	16/75 (21.3)	60/245 (24.5)	61/332 (18.4)	82/405 (20.2)	219/1057 (20.7)
Preterm rupture of membranes, *n/N* (%)	36/75 (48.0)	96/245 (39.2)	140/332 (42.2)	148/405 (36.5)	420/1057 (39.7)
Antenatal steroid use, *n/N* (%)	16/75 (21.3)	79/245 (32.2)	137/332 (41.3)	177/405 (43.7)	409/1057 (38.7)
Maternal transport, *n/N* (%)	38/75 (50.7)	151/245 (61.6)	207/331[a] (62.5)	247/402[a] (61.4)	643/1053[a] (61.1)
Outborn, *n/N* (%)	6/75 (8.0)	20/245 (8.2)	31/332 (9.3)	41/405 (10.1)	98/1057 (9.3)
Cesarean delivery, *n/N* (%)	18/75 (24.0)	104/245 (42.4)	218/332 (65.7)	297/405 (73.3)	637/1057 (60.3)
In-hospital morbidities and interventions, *n/N* (%)					
RDS diagnosed	60/74[a] (81.1)	191/245 (78.0)	251/332 (75.6)	309/405 (76.3)	811/1056[a] (76.8)
CLD at 36 weeks[b]	15/71[a] (21.1)	71/236[a] (30.1)	121/319[a] (37.9)	133/392[a] (33.9)	340/1018[a] (33.4)
PDA ligation	4/72[a] (5.6)	34/238[a] (14.3)	50/316[a] (15.8)	41/389[a] (10.5)	129/1015[a] (12.7)
Neonatal seizure	11/74[a] (14.9)	28/245 (11.4)	40/331[a] (12.1)	30/405 (7.4)	109/1055[a] (10.3)
IVH grade 3–4	18/74[a] (24.3)	52/241[a] (21.6)	48/328[a] (14.6)	49/403[a] (12.2)	167/1046[a] (16.0)
Cystic PVL	2/74[a] (2.7)	10/244[a] (4.1)	13/331[a] (3.9)	22/405 (5.4)	47/1054[a] (4.5)
Sepsis	17/74[a] (23.0)	58/244[a] (23.8)	73/331[a] (22.1)	59/405 (14.6)	207/1054[a] (19.6)
Necrotizing enterocolitis	1/74[a] (1.4)	16/245 (6.5)	10/331[a] (3.0)	15/405 (3.7)	42/1055[a] (4.0)
ROP requiring treatment	15/75[a] (20.0)	73/245 (29.8)	102/331[a] (30.8)	128/405 (31.6)	318/1056[a] (30.1)

BW, birth weight; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome.

[a] There were cases without data on this characteristic.

[b] CLD at 36 weeks was defined when an infant received supplemental oxygen at the postmenstrual age of 36 weeks.

TABLE 2 Neurodevelopmental Outcomes at 3 Years of Age According to Gestational Age

	Gestational Age				
	22 Weeks	23 Weeks	24 Weeks	25 Weeks	Total
Evaluated at 3 years, *n*	23	119	180	240	562
CP, *n/N* (%)[a]	5/23 (21.7)	21/118[b] (17.8)	14/173[b] (8.1)	35/234[b] (15.0)	75/548 (13.7)
Profound CP	4/23 (17.4)	12/118[b] (10.2)	9/173[b] (5.2)	20/234[b] (8.5)	45/548 (8.2)
Hearing impairment, *n/N* (%)[a]	0/23 (0.0)	4/119 (3.4)	2/168[b] (1.2)	3/234[b] (1.3)	9/544 (1.7)
Visual impairment, *n/N* (%)[a]	2/23 (8.7)	12/118[b] (10.2)	6/175[b] (3.4)	5/231[b] (2.2)	25/547 (4.6)
Cognitive delay, *n/N* (%)[a]	12/21[b] (57.1)	55/110[b] (50.0)	49/152[b] (32.2)	58/208[b] (27.9)	174/491 (35.4)
KSPD DQ of 50–69	5/11 (45.5)	12/58 (20.7)	27/104 (26.0)	31/145 (21.4)	75/318 (23.6)
KSPD DQ of <50	0/11 (0.0)	7/58 (12.1)	11/104 (10.6)	17/145 (11.7)	35/318 (11.0)
Judgment of delay by pediatrician	7/10 (70.0)	36/52 (69.2)	11/48 (22.9)	10/63 (15.9)	64/173 (37.0)
NDI, *n/N* (%)[a]	12/23 (52.2)	65/114[b] (57.0)	53/142[b] (37.3)	78/212[b] (36.8)	208/491 (42.4)
Profound NDI	7/23 (30.4)	45/114[b] (39.5)	23/142[b] (16.2)	36/212[b] (17.0)	111/491 (22.6)
Death or NDI, *n/N* (%)[c]	60/75 (80.0)	156/245 (63.7)	129/332 (38.9)	138/405 (34.1)	483/1057 (45.7)
Death or Profound NDI	55/75 (73.3)	136/245 (55.5)	99/332 (29.8)	96/405 (23.7)	386/1057 (36.5)
Unimpaired/minimally impaired, *n/N* (%)[c]	9/75 (12.0)	49/245 (20.0)	89/332 (26.8)	134/405 (33.1)	281/1057 (26.6)

Profound CP was defined as a GMFCS level of 4 or 5. Children who were defined as GMFCS level 1 were excluded and were included in the minimally impaired group. Hearing impairment was defined as requiring amplification. Visual impairment was defined as blind with no functional vision in 1 or both eyes. Cognitive delay was defined as a DQ score <70; if the child was unable to complete the KSPD assessment, the pediatrician estimated the child's developmental level as delayed or not. In cases judged as delayed, the developmental level was assumed to be equivalent to a KSPD DQ of <50. NDI was defined as any of the following: CP with a GMFCS level of 2 to 5, hearing impairment, visual impairment, or DQ score <70. Profound NDI was defined as profound CP and/or a DQ score of <50. Children with an unknown CP level were classified into profound impairment.

[a] (%): percentage of infants with data of the assessment.

[b] There were cases without the assessment.

[c] (%): percentage of the study population.

including 45 (8.2%) with profound CP. Profound CP was more often found in infants born at 22 weeks than in those born at the other weeks. There was no obvious association between hearing impairment and increasing gestational weeks. The proportions with visual impairment were equally high at 22 and 23 weeks. Cognitive delay was found in 174 (35.4%) of the 491 evaluated infants, 75 (15.3%) with a DQ between 50 and 69, and 99 (20.2%) with a DQ ≤50. Of the 318 infants assessed by the KSPD, 20 (6.3%) had a DQ <50 and 75 (23.6%) had a DQ of 50 to 70. In infants with 22 and 23 weeks' gestational age, those whose cognitive function was assessed by pediatricians were more likely to

have blindness (19%) or CP (37%) than infants assessed by the KSPD (3% for blindness and 9% for CP). A total of 208 (42.4%) fully evaluated infants had NDI, with 111 (22.6%) having profound NDI. The incidences of both death or NDI and death or profound NDI were clearly related to gestational weeks. Overall, 281 (26.6%) of the 1057 subjects were unimpaired or minimally impaired at 3 years of age: 9 (12.0%) of whom were born at 22 weeks' gestational age, 49 (20.0%) of whom were born at 23 weeks' gestational age, 89 (26.8%) of whom were born at 24 weeks' gestational age, and 134 (33.1%) of whom were born at 25 weeks' gestational age.

In logistic regression after adjusting for biological and perinatal variables, being born at 22 weeks (OR: 5.40; 95% CI: 2.48–11.76) and 23 weeks (OR: 2.14; 95% CI: 1.38–3.32) in comparison with the reference (24 weeks) increased the risk of death or NDI, but being born at 25 weeks (OR: 0.65; 95% CI: 0.45–0.95) decreased the risk of death or NDI. When infants with birth weights <400 g were excluded from the model to eliminate the effect of severe growth restriction, a gestational age of 22 weeks (OR: 5.77; 95% CI: 2.55–13.04) and 23 weeks (OR: 2.22; 95% CI: 1.43–3.44) compared with a gestational age of 24 weeks similarly increased the risk of death or NDI.

From the systematic review, 46 publications reporting outcomes and follow-up rates were identified, 30 of which described outcomes at 18 to 42 months; however, only 12 included the numbers of cases of death and NDI at 18 to 42 months for a total of 15 different cohorts. Eight of these 15 cohorts contained data that met the definition of NDI in this study. The numbers of cases of death, NDI, and evaluated infants were reported for a total of 9717 extremely premature infants at 18 to 42 months for all 8 publications.[7–18] Year, country of birth, and type of study cohort are summarized in Table 3 and 4 by gestational weeks. Mortality rates ranged from 64% to 100% in infants born at 22 weeks' gestation, from 37% to 100% at 23 weeks' gestation, and from 19% to 65% at 24 to 27 weeks' gestation. Follow-up rates ranged from 0% to 100% for 22 and 23 weeks' gestation and from 70% to 99% for 24 to 27 weeks' gestation (Table 3). The incidence of death or NDI ranged from 80% to 100% for 22 weeks' gestational age, from 64% to 100% for 23 weeks' gestational age, and from 36% to 82% for 24 to 27 weeks' gestational age (Table 4).

DISCUSSION

In a large cohort of extremely preterm infants born at <26 weeks' gestational age, we found that 50% to 60% of survivors born at 22 and 23 weeks' gestational age and ~30% of survivors at 24 and 25 weeks' gestational age had disability at 3 years of age in terms of mental and psychomotor development. On the other hand, nearly half of the infants born even at 22 or 23 weeks, and who had survived to 3 years of age, were unimpaired or minimally impaired, although these proportions were lower than those for infants born at 24 or 25 weeks. The incidence of death or NDI was clearly related to gestational weeks, consistent with many previous studies.[3,5–21] Among the survivors, however, the incidence of NDI for those born at 22 weeks was nearly equal to that for those born at 23 weeks. This result was probably affected by the high mortality for 22 weeks, meaning that the most severe cases born at 22 weeks died early in life. In addition, the proportion of NDI at 22 weeks should be interpreted with caution because the number of survivors in this category was low.

The strengths of our study include the relatively large population with a lower mortality rate of infants born at 22 and 23 weeks than in previous studies, as shown in Table 3. As a result, more infants survived and could be evaluated at 3 years of age.

In the evaluated infants, the proportions of CP, hearing impairment, visual impairment, and a DQ <70 were similar to those in previous studies.[7,11,15,19] The incidence of profound CP was slightly higher than in a report from the NICHD, especially at 22 and 23 weeks.[7] One reason for this was that we classified the infants with an unknown CP level as having profound impairment. We decided to choose the strictest judgment for NDI because the judgment might have a major impact on the conclusion of the study. If the infants with an unknown CP level were excluded from the profound impairment group, the incidence of profound CP decreased to 2 (8.7%) for those born at 22 weeks and to 10 (8.5%) for those born at 23 weeks, which is equal to the incidence in the NICHD data.[7]

The proportion of infants with a DQ <70 was higher than the proportions with other impairments. Approximately half of the infants born at 22 and 23 weeks' gestation were found to have cognitive delay, but the corresponding proportion was one-third at 24 and 25 weeks' gestation. Infants at 22 and 23 weeks were more likely to be judged by a pediatrician and they more often had other handicaps such as blindness or CP. These impairments might prevent completion of the KSPD test.[13] Because pediatricians were not always blinded to perinatal and neonatal morbidities and interventions, judgment by a pediatrician without a test could result in overestimation of the proportion of cognitive delay in infants at 22 and 23 weeks' gestational age. A higher incidence of impaired cognitive development in infants born at very low gestational ages has been described in several reports.[7,11,13,15–21,25] Although

TABLE 3 Survival and Neurodevelopmental Outcomes of Infants Born at 22 and 23 Weeks' Gestation From the Systematic Review

Study Name (Reference) (Location, Age at Follow-up, Year of Birth, Type of Study)	22 Weeks			23 Weeks			24–27 Weeks		
	Mortality,[a] *n*/Live Births (%)	Evaluated, *n*/Survivors at 3 Years (%)	Death or NDI, *n*/Study Cohort (%)	Mortality,[a] *n*/Live Births (%)	Evaluated, *n*/Survivors at 3 Years (%)	Death or NDI, *n*/Study Cohort (%)	Mortality,[a] *n*/Live Births (%)	Evaluated, *n*/Survivors at 3 Years (%)	Death or NDI, *n*/Study Cohort (%)
NICHD (7) (US, 18–24 mo, 2002–2004, multicenter)	309/322 (96)	—	—	342/441 (78)	22–23 weeks; 104/112 (93)	22–23 weeks; 750/763 (98)	24 weeks; 294/632 (47)	22–24 weeks; 405/450 (90)	24 weeks; 489/632 (77)
VON (8) (US, 18–24 mo, 1998–2003, multicenter)	<23 weeks; 504/528 (96)	<23 weeks; 15/21 (71)	<23 weeks; 515/528 (98)	567/916 (62)	214/298 (72)	679/916 (74)	24–25 weeks; 906/3033 (30)	24–25 weeks; 1229/1702 (72)	24–25 weeks; 1401/3033 (46)
Victoria (9,10) (Australia, 24 mo, 2005, population-based)	32/33 (97)	—	—	28/35 (80)	—	—	24–27 weeks; 56/220 (25)	22–27 weeks; 163/172 (95)	22–27 weeks; 196/288 (68)
EPIBEL (11,12) (Belgium,30–42 mo, 1999–2000, population-based)	28/28 (100)	0/0 (0)	28/28(100)	40/41 (98)	1/1(100)	40/41 (98)	24–26 weeks; 91/182 (50)	24–26 weeks; 88/91 (97)	24–26 weeks; 142/182 (78)
EPICure (13,14) (UK, 30 mo median, 1995, population-based)	136/138 (99)	2/2 (100)	137/138(99)	216/241 (90)	25/25(100)	230/241 (95)	24–25 weeks; 525/806 (65)	24–25 weeks; 279/281 (99)	24–25 weeks; 661/806 (82)
EPIPAGE (15,16) (France, 24 mo, 1997, population-based)	16/16 (100)	0/0 (0)	16/16(100)	30/30 (100)	0/0 (0)	30/30 (100)	24–27 weeks; 224/549 (41)	—	—
Essen (17) (Germany, 24–30 mo, 2000–2004, hospital-based)	8/10 (80)	2/2 (100)	9/10(90)	12/18 (67)	5/6 (83)	12/18(67)	24–25 weeks; 16/55 (29)	24–25 weeks; 34/39 (87)	24–25 weeks; 22/55 (40)
ETFOL (18) (Denmark, 24 mo, 1994–1995, population-based)	—	—	—	<24 weeks; 37/37 (100)	<24 weeks; 0/0 (0)	< 24 weeks; 37/37 (100)	24–27 weeks; 154/349 (44)	24–27 weeks; 193/195 (94)	24–27 weeks; 206/349 (59)
Current study (Japan, 36 mo median, 2003–2005, multicenter)	48/75 (64), 43/69 (62)[b]	23/27 (85)	60/75(80)	91/245 (37), 82/225 (36)[b]	119/154 (77)	156/245 (64)	24–25 weeks; 139/737 (19), 127/605(19)[b]	24–25 weeks; 420/601 (70)	24–25 weeks; 267/737 (36)

EPIBEL, Extremely Preterm Infants in Belgium Study Group; EPICure, study for all infants born before 26 completed weeks of gestational age in the United Kingdom and the Republic of Ireland in 1995; EPIPAGE, The Etude Epidémiologique sur les Petits Ages Gestationnels study; VON, Vermont Oxford Network; —, data was not shown.

[a] Mortality included cases who died in the delivery room, died in the NICU, or died after discharge until evaluation, but not cases who died intrapartum.

[b] Mortality excluding the infants transferred after birth to the participating centers from cases in footnote a.

the reason is unclear, various factors affect cognitive development, such as socioeconomic, environmental, and nutritional factors.[8,19,20,34,37] It could be assumed that extreme prematurity of the brain itself is critical for later brain functions.[39–41] Cognitive delay judged by pediatricians may have overestimated the number of infants with a DQ <50.

The most important result in this study was the proportion of unimpaired/minimally impaired infants: 9 (12.0%) of those born at 22 weeks and 49 (20.0%) of those born at 23 weeks. The risks of death or NDI were 5 times higher at 22 weeks' gestational age and 2 times higher at 23 weeks' gestational age than in those born at 24 weeks in a logistic regression model. Resuscitation or intensive care of infants born at 22 or 23 weeks is a very controversial issue.[2,4,7,10,12,20] There is widespread consensus that the aim of neonatal resuscitation should be the qualitatively acceptable survival of the child. However, the guidelines for resuscitation of these infants have not been unified across countries or institutions.[4,22–25,42,43] There could be differences in medical behavior and attitudes associated with the different cultural, social, and legal backgrounds of each country; this could affect the survival and morbidity data of infants born at the threshold of viability. Comparing death or NDI with that in other cohorts, the mortality rate in this study was lower, especially at 22 and 23 weeks, although eligibility and exclusion criteria and the follow-up rate of the study cohorts were not all the same. The incidence of death or NDI was also low, meaning that the proportion of survivors with NDI at 3 years of age was not higher. The follow-up rate, however, may have affected the proportion of NDI, the same as in studies of Mercier et al[8] and Kutz et al.[17] We chose the strictest criteria

TABLE 4 CP and Cognitive Delay of the Evaluated Infants Born at 22 and 23 Weeks' Gestation From the Systematic Review

Study Name (Reference) (Location, Age at Follow-up, Year of Birth, Type of Study)	22 Weeks			23 Weeks			24–27 Weeks		
	CP, *n*/Evaluated Infants (%)	Cognitive Delay, *n*/Evaluated Infants (%)	NDI, *n*/Evaluated Infants (%)	CP, *n*/Evaluated Infants (%)	Cognitive Delay, *n*/Evaluated Infants (%)	NDI, *n*/Evaluated Infants (%)	CP, *n*/Evaluated Infants (%)	Cognitive Delay, *n*/Evaluated Infants (%)	NDI, *n*/Evaluated Infants (%)
NICHD (7) (US, 18–24 mo, 2002–2004, multicenter)	—	—	—	22–23 weeks; 28/105 (27)	22–23 weeks; MDI <70: 63/102 (62); PDI <70: 46/104 (44)	22–23 weeks; 72/103 (70)	24 weeks; 57/298 (19)	24 weeks; MDI <70: 133/282 (47); PDI <70 88/280 (31)	24 weeks; 155/294 (55)
VON (8) (US, 18–24 mo, 1998–2003, multicenter)	<23 weeks CP and/or cognitive delay; 11/15(73)		<23-weeks; 11/15 (13)	CP and/or cognitive delay; 112/214 (52)		112/214 (52)	24–25 weeks CP and/or cognitive delay; 495/1498 (33)		24–25 weeks; 495/1229 (40)
Victoria (9,10) (Australia, 24 mo, 2005, population-based)	—	—	—	—	—	—	22–27 weeks; 16/163 (10)	22–27 weeks; 26/163 (16)	24–27 weeks; 80/163 (49)
EPIBEL (11,12) (Belgium, 30–42 mo, 1999–2000, population-based)	(All cases dead)	(All cases dead)	(All cases dead)	0/1 (0)	0/1 (0)	0/1 (0)	24–26 weeks; 19/77 (25)	24-26 weeks; MDI <70: 22/77 (29); PDI <70: 37/77 (48)	24–26 weeks; 51/88 (58)
EPICure 1 (13,14) (UK, 30 mo median, 1995, population-based)	—	—	1/2 (50)	—	22–23 weeks; 7/26 (27)	14/25 (56)	22–25 weeks; 50/306 (16)	24–25 weeks; 78/257 (30)	24–25 weeks; 136/279 (49)
EPIPAGE (15,16) (France, 24 mo, 1997, population-based)	(All cases dead)	(All cases dead)	(All cases dead)	(All cases dead)	(All cases dead)	(All cases dead)	—	—	—
Essen (17) (Germany, 24–30 mo, 2000–2004, hospital-based)	—	—	1/2 (50)	—	—	0/5 (0)	—	—	24-25 weeks; 6/34 (18)
ETFOL (18) (Denmark, 24 mo, 1994–1995, population-based)	—	—	—	(All cases dead)	(All cases dead)	(All cases dead)	24–27 weeks; 5/53 (9)	24–27 weeks; 9/53 (17)	24–27 weeks; 52/183 (28)
Current study (Japan, 36 mo median, 2003–2005, multicenter)	5/23 (22)	12/21 (57)	12/23 (52)	21/118 (18)	55/110 (50)	65/114 (57)	24–25 weeks; 49/407 (12)	24–25 weeks; 107/360 (30)	24–25 weeks; 131/354 (37)

EPIBEL, Extremely Preterm Infants in Belgium Study Group; EPICure, study for all infants born before 26 completed weeks of gestational age in the United Kingdom and the Republic of Ireland in 1995; EPIPAGE, The Etude Epidémiologique sur les Petits Ages Gestationnels study; MDI, mental developmental index; PDI, psychomotor developmental index; VON, Vermont Oxford Network; —, data was not shown.

for NDI, meaning that impairments having CP or cognitive delay without assessment of degrees were considered as profound impairments. When discussing intervention and treatment of infants at the threshold of viability, we should not do opportunistic assessment because severe impairments would have a major impact on the surviving infants and their parents for life. This strictest criteria for NDI could provide overestimated impairments and the possible-worst outcome. Although there is no definite consensus regarding what probability of survival without profound impairment justifies intensive care,[44] the results of this study provide important information to consider in current treatment.

There are several limitations to this study. The first concerns the follow-up rate, which was ~70% in infants born at 24 and 25 weeks' gestation. It is unclear how the follow-up rate affects the true incidence of severe disability.[45,46] Several reports on attrition in follow-up programs suggest that infants with serious developmental delays or disabilities are more likely to drop out of follow-up.[47–49] Coincident with this, the nonevaluated group had a higher percentage of IVH grade 3–4 than did the evaluated group. This could be relevant and confer a higher risk of NDI in the infants.

The second limitation is a lack of registration of stillbirth and clear classifications of withdrawing/withholding intensive care in the delivery room, which are important when we compare the survival rate with those in other cohort studies.[21] The network defines stillbirth as an infant who does not show any cardiac pulse under vigorous resuscitation after 22 weeks of gestational age regardless of birth weight, although the number of stillbirths was not collected, which remained almost constant at <1% of the total number of infants registered each year.[6] The

numbers of stillbirths or deaths in the delivery room in hospitals other than the participating centers were also not collected. The mortality rate, however, did not change after excluding the outborn infants in this study, as shown in Table 3.

The last limitation concerns the use of the KSPD test for cognitive evaluation. Although the KSPD test is written only in Japanese, it is a validated and standardized developmental test battery available for all centers participating in the follow-up study in Japan.[32] KSPD assessment is not comparable to, for instance, the Bayley Scales of Infant Development III, which is widely used for cognitive evaluation at this age.[50] Additionally, we could not collect socioeconomic information, which is known to be associated with infants' future developmental state.[51] The quality of life of the infants, their later neurologic outcomes, and academic and social achievements into adulthood should also be elucidated in future studies.

CONCLUSIONS

Infants born at 22 and 23 weeks' gestation were at higher risk of death or NDI than infants born at 24 and 25 weeks' gestation, but outcomes were improved compared with those in previous studies from a systematic review. There is a need for additional discussions on interventions for infants born at 22 or 23 weeks' gestation.

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A GLANCE INTO THE FUTURE: FECAL TRANSPLANTS FOR WEIGHT LOSS: *Each day I am bombarded with information about how to lose weight. There seems to be an almost endless array of diet or exercise recommendations and oodles of gadgets "guaranteed" to work. In the past few months, one of my relatives has tried to lose weight following the South Beach diet, then a Paleolithic diet, and most recently using a smart phone application. Maybe she should try a fecal transplant. As reported in* The New York Times *(Health: March 28, 2013), the bacterial flora in our guts may be at least partially responsible for weight loss or gain. Researchers have never quite understood all the reasons why people lose weight following gastric bypass surgery. However, in a recent study conducted in mice, researchers concluded that approximately 20% of the weight loss is most likely due to a change in bacterial flora. Fattened mice that underwent gastric bypass surgery lost weight and had altered intestinal flora. Mice that underwent a sham surgery where the intestine was simply severed and re-anastomosed did not lose weight and the microbiota did not change. Next, intestinal contents from each group were transplanted into mice lacking intestinal flora. The mice that received material from the bypass surgery group lost weight while the mice receiving material from the sham group did not. In a study conducted in adults with potential gastrointestinal disorders, researchers found that indirect evidence of the presence of* Methanobrevibacter smithii *in the gut was directly related to body mass. The individuals with the highest levels of methane and hydrogen on breath tests were more likely to have more body fat. One possible explanation for this finding is that* M. smithii *may contribute to the breakdown of foodstuffs, making more calories available. The general dieter may not be ready for a fecal transplant to help increase weight loss, but the more we learn about our gut and the bacteria that inhabit it, the more we realize how intertwined we are.*

Noted by WVR, MD