Published by Oxford University Press on behalf of the International Epidemiological Association
International Journal of Epidemiology 2011;**40**:611–618
doi:10.1093/ije/dyq071
© The Author 2010; all rights reserved. Advance Access publication 26 May 2010

COHORT PROFILE

Cohort Profile: The Hokkaido Study on Environment and Children's Health in Japan

Reiko Kishi,[1]* Seiko Sasaki,[1] Eiji Yoshioka,[1] Motoyuki Yuasa,[2] Fumihiro Sata,[3] Yasuaki Saijo,[4] Norie Kurahashi,[5] Junko Tamaki,[6] Toshiaki Endo,[7] Kazuo Sengoku,[8] Katsuya Nonomura[9] and Hisanori Minakami,[10] for the Hokkaido Study on Environment and Children's Health[†]

[1]Department of Public Health Sciences, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]Department of Public Health, School of Medicine, Juntendo University, Tokyo, Japan, [3]Department of Epidemiology, National Institute of Public Health, Wako, Japan, [4]Department of Health Science, School of Medicine, Asahikawa Medical College, Asahikawa, Japan, [5]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan, [6]Department of Public Health, School of Medicine, Kinki University, Osaka, Japan, [7]Department of Obstetrics and Gynecology, School of Medicine, Sapporo Medical University, Sapporo, Japan, [8]Department of Obstetrics and Gynecology, School of Medicine, Asahikawa Medical College, Asahikawa, Japan, [9]Department of Renal and Genitourinary Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan and [10]Department of Obstetrics and Gynecology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

*Corresponding author. Department of Public Health Sciences, Hokkaido University Graduate School of Medicine, North 15 West 7, Kita-ku, Sapporo 060-8638, Japan. E-mail: rkishi@med.hokudai.ac.jp
[†]The members of the Hokkaido Study on Environment and Children's Health are listed in Appendix 1

Accepted 24 March 2010

How did the study come about?

The Hokkaido study of Environment and Children's Health is an ongoing cohort study that began in 2002. The study consists of two prospective birth cohorts: the Toho hospital cohort with one obstetric hospital in Sapporo City, and the Hokkaido large-scale cohort with 37 hospitals and clinics in Hokkaido prefecture. Hokkaido is the northernmost and the second largest island of Japan: it has an area of ~78 417 km^2, equivalent to that of Austria. Its population is 5 546 559, which is similar to that of Finland.

Persistent organic pollutants (POPs) including polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs), as well as perfluorooctanoate sulphonate (PFOS) and perfluorooctanoate (PFOA), the final metabolites of fluorinated organic compounds (FOCs), may accumulate in the human body. These environmental chemicals may contribute to numerous adverse health effects including growth retardation of fetuses and infants, disturbances of the neurodevelopment, thyroid, immune and reproductive systems and may exert genetic or epigenetic effects when metabolized. In the USA, lower level PCB exposure during pregnancy was associated with decreased birth weight.[1–3] In Finland, total toxic equivalent (TEQ) levels of PCDDs/PCDFs in breast milk negatively correlated with birth weight, especially of boys.[4] In a Dutch report, negative effects of prenatal dioxin and PCB exposure on cognitive and motor development were found in school-age children.[5] An assessment of childhood play behaviour at 9 years of age correlated higher prenatal PCB levels with less masculinized play in boys and with more masculinized play in girls. Higher prenatal dioxin levels were associated with more feminized play in both boys and girls.[6] Concerning the immunological effects of environmental exposure, prenatal PCB exposure was associated with less shortness of breath with wheezing; postnatal PCB exposure was associated with a higher prevalence of recurrent otitis media.[7,8] Two studies reported correlations between prenatal PFOS/PFOA exposure and reduced birth weight.[9,10]

Congenital malformations such as hypospadias are speculated to be related to genetic variations in the synthesis and metabolism of steroids combined with environmental factors. Hypospadias are a common congenital malformation caused by incomplete fusion of the urethral folds. Recently, a number of reports indicate an increased prevalence of hypospadias in various countries including Japan; this trend is speculated to be related to endocrine-disrupting chemicals.[11] Previous studies were limited to assess either genetic or environmental contributions to its etiology; for example, case–control studies reported genetic polymorphisms associated with hypospadias and nested case–control studies reported an association of hypospadias with agricultural exposures.[12–15]

Downloaded from https://academic.oup.com/ije/article/40/3/611/738972 by U.S. Department of Justice user on 16 August 2022

Several birth cohorts have been established worldwide in recent years; however, few reports have been published on the relationship between low-level environmental exposures and adverse birth outcomes. In the field of infant development, variations in the human genome and their modifications on the effect of hazardous environmental exposures (gene–environment interaction) have not been thoroughly investigated.

The study was established to investigate the effects of environmental exposure combined with genetic predisposition in the development and health in prenatal period, infancy and early childhood.[16]

What does the study cover?

The aims of the study are the following: (i) to examine possible negative effects of perinatal environmental factors on birth outcomes including congenital anomalies and growth retardation; (ii) to follow the prevalence of allergic diseases or neurodevelopmental disorders, and perform longitudinal observation of child development; (iii) to identify a high-risk group classified by genetic susceptibility to environmental chemicals; and (iv) to identify additive effects of various chemicals encountered in the daily environment.

In particular, the Toho hospital cohort has focused on the association between child growth, neurodevelopment and allergy, and low-level exposure to environmental chemicals during pregnancy and infancy. The Hokkaido large-scale cohort was established primarily to assess the prevalence of congenital anomalies including cleft lip and plate, congenital heart defects, hypospadias and cryptorchidism, and has explored the possible causes of these malformations. This cohort also follows the prevalence of childhood allergies and neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD).

Who are in the sample?

The Institutional Ethical Board for Human Gene and Genome studies at Hokkaido University Graduate School of Medicine approved the study protocol. The study was conducted with the informed consent of all subjects. The enrolment of the Toho hospital cohort was conducted from July 2002 to October 2005. Of 1796 potentially eligible women, 514 agreed to participate. The subjects were women who enrolled at 23–35 weeks of gestation and delivered at the Toho hospital. All the subjects were resident in Sapporo City or surrounding areas. Since February 2003, the Hokkaido large-scale cohort has conducted enrolment of women in early pregnancy (<13 weeks of gestational age) that visited one of associated hospitals or clinics in the study area for prenatal health care at the maternity unit. The total number of infants whose congenital anomalies were surveyed in the cohort was 9335 until 2006. This cohort will consist of 20 000 children. Each cohort will follow its participants up to school age.

What has been measured?

The protocol for study design and exposure measurement items is presented in Figures 1 and 2, and Table 1.

In the Toho hospital cohort, a self-administered questionnaire was completed at the time of enrolment to obtain baseline information including parental demographic characteristics, dietary habits including the amount and species of fish consumed, exposure to chemical compounds in their daily life, smoking history, alcohol consumption, caffeine intake and household income. Information on pregnancy complications, gestational age at birth, infant gender and birth size was obtained from maternal and infant medical records. Maternal blood samples were

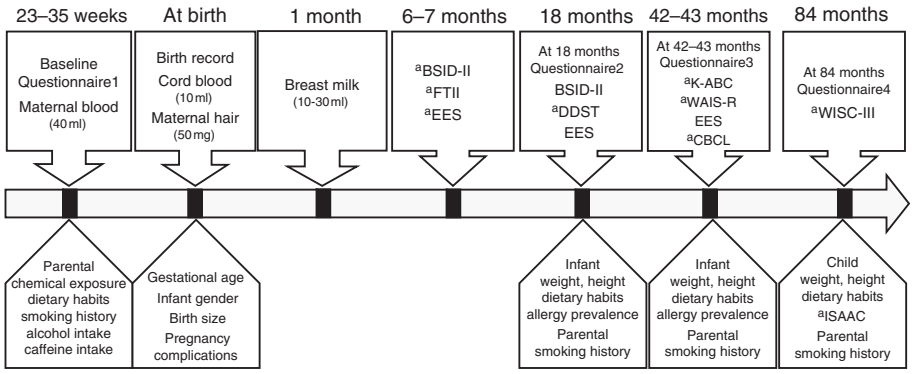

Figure 1 Study design of the Toho hospital cohort. BSID-II: The Bayley Scales of Infant Development second edition; FTII: The Fagan Test of Infant Intelligence; K-ABC: The Kaufman Assessment Battery for Children; WAIS-R: The Wechsler Adult Intelligence Scale-Revised; WISC-III: The Wechsler Intelligence Scale for Children third edition; EES: The Evaluation of Environmental Stimulation; DDST: The Denver Developmental Screening Tests; CBCL, the Child Behaviour Checklist; ISAAC: International Study of Asthma and Allergies in Childhood

Downloaded from https://academic.oup.com/ije/article/40/3/611/738972 by U.S. Department of Justice user on 16 August 2022

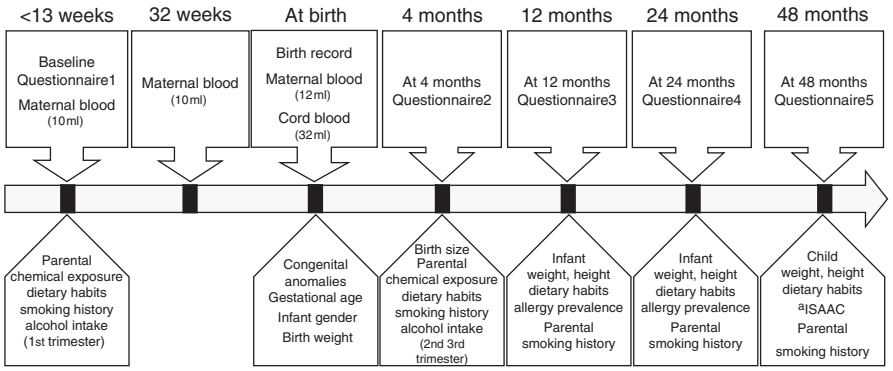

Figure 2 Study design of the Hokkaido large-scale cohort. ISAAC: International Study of Asthma and Allergies in Childhood

Table 1 Items measured in the Hokkaido study of Environment and Children's Health

Measurement	Description
Exposure measurement	
PCDDs, PCDFs	Maternal blood, cord blood and breast milk
PCBs	Maternal blood, cord blood and breast milk
OH-PCBs	Maternal blood, cord blood and breast milk
PFOS, PFOA	Maternal blood, cord blood and breast milk
BPA, NP	Maternal blood, cord blood and breast milk
DEHP	Maternal blood, cord blood, and breast milk
Pesticides	Maternal blood, cord blood and breast milk
Heavy metals	Maternal blood, cord blood and breast milk
MeHg	Maternal blood, cord blood and maternal hair
Cotinine	Maternal blood, cord blood and maternal hair
Other biochemical measurements	
TSH, FT4	Maternal blood and infant blood
Folic acid	Maternal blood and cord blood
IgE, IgA	Cord blood

OH-PCBs: hydroxylated polychlorinated biphenyls; BPA: bisphenol A; NP: nonylphenol; DEHP: Di(2-ethylhexyl)phthalate; MeHg: methylmercury; TSH: thyroid stimulating hormone; FT4: free thyroxine.

collected in late pregnancy, usually after the 30th week of gestation. Cord blood and placenta were taken immediately after birth. Maternal hair samples were also collected within 5 days after delivery, and breast milk from nursing mothers was collected within 4 weeks following birth.

The levels of PCDDs/PCDFs and PCBs in maternal blood and breast milk were measured using a high-resolution gas chromatography/high-resolution mass spectrometre (HRGC/HRMS) at Fukuoka Institute of Health and Environmental Sciences.[17–20] PFOS and PFOA levels in maternal blood, cord blood and breast milk were analysed by liquid chromatography-tandem mass spectrometry (LC/MS/MS) at Hoshi University.[21,22] Total mercury levels in maternal hair samples were measured by an oxygen combustion–gold amalgamation method using an atomic absorption detector at National Institute for Minamata Disease.[23] Cord serum immunoglobulin E (IgE) and immunoglobulin A (IgA) were also determined. In order to avoid the possibility of maternal blood contamination, we regarded any cord serum IgA > 10 mg/dl sample as inappropriate. Thyroid stimulating hormone (TSH) and FT4 levels of mother and newborn were measured as a mass screening programme in Sapporo City. For these examinations, a maternal blood sample was collected in the first trimester and a neonate blood sample on filter paper was collected between 4 and 7 days of age. Maternal serum cotinine concentration in maternal blood was

Downloaded from https://academic.oup.com/ije/article/40/3/611/738972 by U.S. Department of Justice user on 16 August 2022

measured using an enzyme-linked immunosorbent assay (ELISA) kit to evaluate smoking exposure levels. Genetic polymorphisms were determined by means of the TaqMan (Applied Biosystems, Inc., Foster City, CA, USA) polymerase chain reaction (PCR) method, using minor groove binder (MGB) probes.

A follow-up questionnaire was also used at 18, 42 and 84 months of age to obtain relevant information including allergy prevalence, dietary habits and smoking history of mother and the partner. In addition, the Toho hospital cohort has assessed the influence of low-level intrauterine exposure of toxic chemicals on childhood neurodevelopment. The Bayley Scales of Infant Development second edition (BSID-II) was used to at 6–7 and 18 months of age. The Fagan Test of Infant Intelligence (FTII) was performed to measure visual recognition memory and cognitive ability on infants aged 6–7 months. To examine developmental progress, the Japanese version of the Denver Developmental Screening Tests (DDST) was used at age 18 months. At 42 months of age, child and maternal intelligence were measured by Japanese version of the Kaufman Assessment Battery for Children (K-ABC) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R), respectively. The Wechsler Intelligence Scale for Children third edition (WISC-III) was used to assess the attention and motor function of children at 84 months of age. The questionnaire of home environment, the Evaluation of Environmental Stimulation (EES), was used to investigate the environmental conditions of children at 6, 18 and 43 months of age. The Japanese version of the Child Behavior Checklist (CBCL) was used to collect information on child behaviour at age 43 months.

In the Hokkaido large-scale cohort, a baseline questionnaire survey was conducted at the time of enrolment during the first trimester to obtain parental information such as demographic characteristics, medical and obstetric history, dietary supplement intake during pregnancy and chemical exposure at work. Perinatal data such as birth weight, infant gender, mode of delivery, multiple births and prevalence of congenital anomalies were obtained from birth records completed by an obstetrician. The congenital anomalies were classified into 55 markers according to the criteria. The first follow-up questionnaire was used on infants at 4 months of age to obtain relevant data including birth size, gestational age at birth and parental smoking history in the second and third trimester. The follow-up questionnaire was administered at age 12, 24 and 48 months to obtain relevant information such as child weight and height measured at regular health checkups, vaccination history, dietary habits, parental smoking history and allergy prevalence using the International Study of Asthma and Allergies in Childhood (ISAAC). The CBCL was used to investigate association between perinatal exposure and developmental disorder. Maternal blood was collected three times: between 6 and 14 weeks of gestational age as an organogenetic period; during the third trimester; and at delivery. Cord blood was taken immediately after birth. Maternal serum was used to measure folic acid level and plasma cotinine concentration.

What has the study found?

A total of 514 mothers were registered in the Toho hospital cohort and 16 306 mothers were registered in the Hokkaido large-scale cohort up to the end of November 2009. Table 2 shows characteristics of mothers and infants in the Toho hospital cohort, and Table 3 shows those of the Hokkaido large-scale cohort. These two cohorts did not show significant difference in characteristics of mothers and infants.

Effects of PCDD/PCDF and dioxin-like PCB exposure on birth weight

We measured 29 congener levels of PCDDs/PCDFs and dioxin-like PCBs in maternal blood to examine an association between these concentrations and infant

Table 2 Characteristics of mothers and infants in the Toho hospital cohort

	$N = 484$ n (%) or mean ± SD
Maternal characteristics	
Age (years)	30.7 ± 4.9
Parity	
0	230 (47.5)
⩾ 1	254 (52.5)
Educational level (years)	
<10	14 (2.9)
10–13	201 (41.5)
13–17	261 (53.9)
⩾ 17	8 (1.7)
Household income (million yen)	
<3	93 (19.2)
3–5	241 (49.8)
⩾ 5	150 (31.0)
Smoking status during pregnancy	
Non-smoker	289 (59.7)
Quitter	105 (21.7)
Smoker	90 (18.6)
Infant characteristics	
Birth weight (g)	3065 ± 375
Gestational age (weeks)	39.0 ± 1.4

SD: standard deviation.

Downloaded from https://academic.oup.com/ije/article/40/3/611/738972 by U.S. Department of Justice user on 16 August 2022

Table 3 Characteristics of mothers and infants in the Hokkaido large-scale cohort

	$N = 2777$ n (%) or mean ± SD
Maternal characteristics	
Age (years)	29.9 ± 4.6
Parity ($n = 2515$)	
0	992 (39.4)
⩾ 1	1523 (60.6)
Educational level (years, $n = 2752$)	
<10	137 (5.0)
10–13	1294 (47.0)
13–17	1089 (39.6)
⩾ 17	232 (8.4)
Household income (million yen, $n = 2297$)	
<3	487 (21.2)
3–5	1055 (45.9)
⩾ 5	755 (32.9)
Smoking status during pregnancy	
Non-smoker	625 (61.5)
Quitter	265 (26.1)
Smoker	126 (12.4)
Infant characteristics	
Birth weight (g)	3041 ± 411
Gestational age (weeks)	38.9 ± 1.5

birth weight in the Toho hospital cohort. The mean TEQ level was 17.5 TEQ pg/g lipid in maternal blood. We found a 272.7-g decrease in birth weight with a 10-fold increase in total PCDF levels [95% confidence interval (CI) −505.8 to −39.5] after adjustment for potential covariates such as infant gender, gestational age, parity, maternal age and maternal smoking status during pregnancy. Total PCDD TEQ (−231.5 g, 95% CI −417.4 to −45.6), total PCDF TEQ (−258.8 g, 95% CI −445.7 to −71.8), total PCDD/PCDF TEQ (−256.4 g, 95% CI −448.6 to −64.2) and total TEQ (−220.5 g, 95% CI −399.2 to −41.9) levels were significantly negatively associated with birth weight among all infants. Among male infants, significant adverse associations with birth weight were found for total PCDD TEQ level, total PCDD/PCDF TEQ level and total TEQ level; however, these significant adverse associations were not found among female infants. Moreover, we found significantly negative association with the levels of 2,3,4,7,8-PeCDF (−24.5 g, 95% CI −387.4 to −61.5). Our findings suggest that prenatal low-level exposure to PCDDs and PCDFs may result in lower birth weight, which may accumulate in the placenta and retard important placental functions.[24]

Effects of PFOS and PFOA exposure on birth weight

We examined a correlation between maternal serum PFOS and PFOA concentrations and infant birth weight in the Toho hospital cohort. Concentrations ranged from 1.3 to 16.2 ng/ml for PFOS and from below the detection limit to 5.3 ng/ml for PFOA (both detection limits were 0.5 ng/ml). A $\log_{10}$-unit increase in PFOS levels correlated with a decrease in birth weight of 148.8 g (95% CI 297.0 to 0.5) after adjusting for confounders; however, no correlation was observed between PFOA levels and birth weight. Our results indicate that *in utero* exposure to relatively low levels of PFOS negatively correlates with birth weight.[25]

Low birth size in relation to maternal smoking and genetic polymorphisms

The effects of maternal smoking and genetic polymorphisms on infant birth size were examined in the Toho hospital cohort. Birth weight and length were significantly lower among infants born to smokers with the aryl hydrocarbon receptor (*AhR*) GG genotype, the cytochrome P-450 1A1 (*CYP1A1*) TC/CC genotype or the glutathione *S*-transferase T1 (*GSTM1*) null genotype. When combinations of these genotypes were considered, birth weight and length were significantly lower for infants of continuously smoking women with the *AhR* GG genotype and *CYP1A1* TC/CC genotype (−315 g and −1.7 cm, respectively) and with the *CYP1A1* TC/CC genotype and *GSTM1* null genotype (−237 g and −1.3 cm, respectively). For polymorphisms in gene-encoding *N*-nitrosamine-metabolizing enzymes -NAD(P)H: quinone oxidoreductase 1 (*NQO1*)- birth weight, birth length and birth head circumference were significantly reduced (−199 g, −0.8 cm and −0.7 cm, respectively) among infants born to smokers with the *NQO1* CC genotype. This genotype did not confer adverse effects among women who had never smoked or who quit smoking during the first trimester. Our results suggest an important modulating role for polymorphisms in metabolizing enzyme genes in concert with adverse effects of maternal smoking on infant birth size.[26,27]

Effects of PCDD/PCDF and dioxin-like PCB exposure on neurodevelopment

We used the BSID-II to evaluate a correlation between maternal PCDD/PCDF and dioxin-like PCB levels and the mental and motor development of their 6-month-old infants in the Toho hospital cohort. The mean mental development index (MDI) and psychomotor development index (PDI) scores were 91.9 and 89.3, respectively. After adjustment for potential confounding variables, total PCDDs, total PCDDs/PCDFs and 1,2,3,4,6,7,8-HpCDD were significantly negatively associated with MDI. Total 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD,

Downloaded from https://academic.oup.com/ije/article/40/3/611/738972 by U.S. Department of Justice user on 16 August 2022

2,3,7,8-TCDF, 1,2,3,7,8-PeCDF and 1,2,3,6,7,8-HxCDF were significantly negatively associated with PDI. However, the total levels of PCDDs/PCDFs and dioxin-like PCBs were not significantly associated with PDI, and the TEQ values were not significantly associated with MDI or PDI. Our results suggest that the low-level exposure of several congeners of PCDDs/PCDFs during pregnancy affect the neurodevelopment of 6-month-old infants.[28]

The prevalence of congenital anomalies

We estimated the prevalence of congenital anomalies in Hokkaido prefecture. Among 9335 infants included in the Hokkaido large-scale cohort between 2003 and 2006, there were 215 infants with congenital anomalies. The most frequent congenital anomaly was congenital heart defects, followed by Down syndrome, hydronephrosis, polydactyly and cryptorchidism (Table 4). The total prevalence of congenital anomalies was similar to nationwide data reported by the Japan Association of Obstetricians & Gynecologists (JAOG); however, the number of serious cases was less than that of the JAOG. Members of JAOG consist of university and tertiary hospitals, whereas those of the Hokkaido Study on Environment and Children's Health are general hospitals and clinics.

What are the main strengths and weaknesses of the study?

The design of our study is a prospective cohort study intended to collect data on environmental exposures during the fetal period and to control for potential confounders. The detailed measurements are adequate to detect various effects of perinatal environmental and genetic determinant on outcomes in childhood. The Toho hospital cohort study has conducted face-to-face examinations for neurodevelopment assessment. The Hokkaido large-scale cohort is the largest birth cohort in Japan. Potential problems with both cohorts include the fact that they are hospital-based studies, which may result in selection bias. Some levels of attrition related to individuals moving outside the study area has occurred, though we send participants periodical newsletters to maintain the profile of study.

Can I get hold of the data?

Additional information about the Hokkaido study is available at the study website: http://www.med.hokudai.ac.jp~pubmed-w/EnglishHP/e%20research%20groups%202.htm. All collected source data are maintained and stored at the Department of Public Health Sciences, Hokkaido University Graduate School of Medicine. Initial approaches or enquiries

Table 4 Prevalence of congenital anomalies in the Hokkaido large-scale cohort (2003–06)

	Hokkaido large-scale cohort (in 10 000 persons)	JAOG (2006) (in 10 000 persons)
Head		
Anencephaly	2.8	–
Microcephaly	0.7	–
Hydrocephaly	2.1	6.5
Holoprosencephaly	1.4	–
Ear		
Microtia	1.4	–
Meatal atresia	1.4	–
Cryptotia	2.1	–
Low-set ears	1.4	10.8
Orofacial		
Cleft lip	4.2	8.4
Cleft plate	4.9	6.4
Cleft lip and cleft plate	7.0	15.1
Upper limb		
Polydactyly	7.7	6.5
Syndactyly	2.8	5.1[b]
Trunk		
Myelomeningocele (spina bifida)	2.1	5.0
Omphalocele	2.1	4.3
Gastroschisis	2.8	–
Other abdominal wall defects	7.7	–
Heart		
Congenital heart disease	26.4	–
Digestive organ		
Esophageal atresia	1.4	–
Anorectal anomaly	3.5	–
Intestinal atresia	2.8	6.8
Doudenal atresia	2.1	–
Urinary and genital organs		
Hydronephrosis	9.0	–
Renal dysplasia	2.8	–
Hypospadias[a]	8.3	3.7[b]
Cryptorchidism[a]	12.5	–
Ambiguous genitalia	5.6	–
Leg		
Polydactyly	2.8	4.7[b]
Syndactyly	2.8	–
Cleft foot	0.7	–
Syndromes or chromosomal aberration		
Down syndrome	9.7	9.7
Trisomy 18 syndrome	2.1	–

Dashes represent data not surveyed.
[a]Male infants only, the prevalence rate shown in the Table is per 10 000 male infants.
[b]Data from 1997 to 2005.

Downloaded from https://academic.oup.com/ije/article/40/3/611/738972 by U.S. Department of Justice user on 16 August 2022

regarding the study can be made to the principal investigator (rkishi@med.hokudai.ac.jp).

Funding

Grant-in-Aid for Scientific Research from the Ministry of Health, Labor and Welfare; the Ministry of Education, Culture, Sports, Science and Technology; and the Japan Society for the Promotion of Science.

Acknowledgements

The authors would like to express special gratitude for all the personnel in hospitals and clinics that collaborated with the study: Aoba Ladies Clinic, Akiyama Memorial Hospital, Asahikawa Medical Collage Hospital, Asahikawa Red Cross Hospital, Engaru-Kosei General Hospital, Endo Kikyo Maternity Clinic, Ohji General Hospital, Obihiro-Kyokai Hospital, Obihiro-Kosei General Hospital, Kitami Red Cross Hospital, Kitami Lady's Clinic, Kin-ikyo Sapporo Hospital, Kushiro Red Cross Hospital, Kushiro Rosai Hospital, Keiai Hospital, Kohnan Hospital, Gorinbashi Hospital, Sapporo City General Hospital, Sapporo Medical University Hospital, Sapporo-Kosei General Hospital, Sapporo Tokushukai Hospital, Shibetsu City General Hospital, Shiroishi Hospital Tenshi Hospital, Nakashibetsu Municipal Hospital, Nakamura Hospital, Nayoro City General Hospital, Nikko Memorial Hospital, Hakodate City Hospital, Hakodate Goryoukaku Hospital, Hakodate Central General Hospital, Hashimoto Clinic, Hoyukai Sapporo Hospital, Hokkaido University Hospital, Memuro Municipal Hospital, Hokkaido Monbetsu Hospital and Wakkanai City Hospital.

References

[1] Karmaus W, Zhu X. Maternal concentration of polychlorinated biphenyls and dichlorodiphenyl dichlorethylene and birth weight in Michigan fish eaters: a cohort study. *Environ Health* 2004;**3:**1.

[2] Hertz-Picciotto I, Charles MJ, James RA, Keller JA, Willman E, Teplin S. In utero polychlorinated biphenyl exposures in relation to fetal and early childhood growth. *Epidemiology* 2005;**16:**648–56.

[3] Sagiv SK, Tolbert PE, Altshul LM *et al*. Organochlorine exposures during pregnancy and infant size at birth. *Epidemiology* 2007;**18:**120–29.

[4] Vartiainen T, Jaakkola JJ, Saarikoski S *et al*. Birth weight and sex of children and the correlation to the body burden of PCDDs/PCDFs and PCBs of the mother. *Environ Health Perspect* 1998;**106:**61–66.

[5] Vreugdenhil HJ, Lanting CI, Mulder PG *et al*. Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. *J Peadiatr* 2002;**140:**48–56.

[6] Vreugdenhil HJ, Slijper FM, Mulder PG *et al*. Effects of perinatal exposure to PCBs and dioxins on play behavior in Dutch children at school age. *Environ Health Perspect* 2002;**110:**593–98.

[7] Weisglas-Kuperus N, Patandin S, Berbers GA *et al*. Immunologic effects of background exposure to poly chlorinated biphenyls and dioxins in Dutch preschool children. *Environ Health Perspect* 2000;**108:**1203–7.

[8] Weisglas-Kuperus N, Vreugdenhil HJ, Mulder PG. Immunological effects of environmental exposure to polychlorinated biphenyls and dioxins in Dutch school children. *Toxicol Lett* 2004;**149:**281–85.

[9] Apelberg BJ, Witter FR, Herbstman JB *et al*. Cord serum concentrations of Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoate (PFOA) in relation to weight and size at birth. *Environ Health Perspect* 2007;**115:**1670–76.

[10] Fei C, McLaughiln JK, Tarone RE, Olsen J. Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort. *Environ Health Perspect* 2007;**115:** 1677–82.

[11] Kurahashi N, Murakumo M, Kakizaki H *et al*. The estimated prevalence of hypospadias in Hokkaido, Japan. *J Epidemiol* 2004;**14:**73–77.

[12] Kurahashi N, Sata F, Kasai S *et al*. Maternal genetic polymorphisms in CYP1A1, GSTM1 and GSTT1 and the risk of hypospadias. *Mol Hum Reprod* 2005;**11:**93–98.

[13] Ban S, Sata F, Kurahashi N *et al*. Genetic polymorphisms of ESR1 and ESR2 that may influence estrogen activity and the risk of hypospadias. *Hum Reprod* 2008;**23:** 1466–71.

[14] Carbone P, Giordano F, Nori F *et al*. The possible role of endocrine disrupting chemicals in the aetiology of cryptorchidism and hypospadias: a population-based case-control study in rural Sicily. *Int J Androl* 2007;**30:** 3–13.

[15] Weidner IS, Moller H, Jensen TK *et al*. Cryptorchidism and hypospadias in sons of gardeners and farmers. *Environ Health Perspect* 1998;**106:**793–96.

[16] Kishi R, Sata F, Yoshioka E *et al*. Exploiting gene-environment interaction to detect adverse health effects of environmental chemicals on the next generation. *Basic Clin Pharmacol Toxicol* 2008;**102:**191–203.

[17] Iida T, Todaka T. Measurement of dioxins in human blood: improvement of analytical method. *Ind Health* 2003;**41:**197–204.

[18] Todaka T, Hirakawa H, Tobiihi K *et al*. New protocol of dioxins analysis in human blood. *Fukuoka Igaku Zasshi* 2003;**94:**148–57.

[19] Todaka T, Hirakawa H, Kajiwara J *et al*. Concentrations of polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and dioxin-like polychlorinated biphenyls in blood collected from 195 pregnant women in Sapporo City, Japan. *Chemosphere* 2007;**69:**1228–37.

[20] Todaka T, Hori T, Hirakawa H *et al*. Congener-specific analysis of non-dioxin-like polychlorinated biphenyls in blood collected from 195 pregnant women in Sapporo City, Japan. *Chemosphere* 2008;**73:**923–31.

[21] Inoue K, Okada F, Ito R *et al*. Perfluorooctane sulfonate (PFOS) and related perfluorinated compounds in human maternal and cord blood samples: assessment of PFOS exposure in a susceptible population during pregnancy. *Environ Health Perspect* 2004;**112:**1204–7.

[22] Inoue K, Okada F, Ito R *et al*. Determination of perfluorooctane sulfonate, perfluorooctanoate and

Downloaded from https://academic.oup.com/ije/article/40/3/611/738972 by U.S. Department of Justice user on 16 August 2022

perfluorooctane sulfonylamide in human plasma by column-switching liquid chromatography-electrospray mass spectrometry coupled with solid-phase extraction. *J Chromatogr B Analyt Technol Biomed Life Sci* 2004;**810:** 49–56.

[23] Konishi K, Sasaki S, Kato S *et al*. Effect of prenatal exposure to dioxins on birth weight. *Persistent Organic Pollutants (POPs) Research in Asia* 2008;362–67.

[24] Konishi K, Sasaki S, Kato S *et al*. Prenatal exposure to PCDDs/PCDFs and dioxin-like PCBs in relation to birth weight. *Environ Res* 2009;**109:**906–13.

[25] Washino N, Saijo Y, Sasaki S *et al*. Correlation between prenatal exposure to perfluorinated chemicals and reduced fetal growth. *Environ Health Perspect* 2009;**117:** 660–67.

[26] Sasaki S, Kondo T, Sata F *et al*. Maternal smoking during pregnancy and genetic polymorphisms in the *Ah* receptor, *CYP1A1* and *GSTM1* affect infant birth size in Japanese subjects. *Mol Hum Reprod* 2006;**12:**77–83.

[27] Sasaki S, Sata F, Katoh S *et al*. Adverse birth outcomes associated with maternal smoking and polymorphisms in the *N*-nitrosamine-metabolizing enzyme genes *NQO1* and *CYP2E1*. *Am J Epidemiol* 2008;**167:**719–26.

[28] Nakajima S, Saijo Y, Kato S *et al*. Effects of prenatal exposure to polychlorinated biphenyls and dioxins on mental and motor development in Japanese children at 6 months of age. *Environ Health Perspect* 2006;**114:** 773–78.

Appendix 1: Members of the Hokkaido Study on Environment and Children's Health

Members of the Hokkaido Study are: Drs K. Cho, T. Yamada, S. Ban, A. Kanazawa, N. Washino, K. Konishi, S. Katoh, A. Uno, T. Baba, T. Yila, C. Miyashita, T. Braimoh, I. Kashino, E. Okada, S. Kobayashi, Y. Otake, and M. Limpar, Hokkaido University Graduate School of Medicine, Sapporo; S. Nakajima and T. Baba, Sapporo Medical University, Sapporo; T. Miyamoto, Asahikawa Medical College, Asahikawa; N. Maeda, Toho Obstetrics & Gynecology Hospital, Sapporo; and H. Haruyama and K. Okuyama, Sapporo City Hospital, Sapporo.

Downloaded from https://academic.oup.com/ije/article/40/3/611/738972 by U.S. Department of Justice user on 16 August 2022