Yila TA, Sasaki S, Miyashita C, Braimoh TS, Kashino I, Kobayashi S, Okada E, Baba T, Yoshioka E, Minakami H, Endo G, Sengoku K, Kishi R.	Effects of maternal 5,10-methylenetetrahydrofolate reductase C677T and A1298C polymorphisms and tobacco smoking on infant birth weight in a Japanese population.	J Epidemiology.			In press
那須民江,岸玲子.	胎生期低栄養と小児の健康.	日本衛生学雑誌.	67(1)	21	2012
Okada E, Sasaki S, Saijo Y, Washino N, Miyashita C, Kobayashi S, Konishi K, Ito YM, Ito R, Nakata A, Iwasaki Y, Saito K, Nakazawa H, Kishi R.	Prenatal exposure to perfluorinated chemicals and relationship with allergies and infectious diseases in infants.	Environ Res.	112(1)	118-125	2012
岸玲子	【地域における母子保健縦断調査の活用】 環境と子どもの健康に関する北海道コーホートの成果と今後の課題.	保健の科学	53(2)	98-104	2011

Todaka T, Hirakawa H, Kajiwara J, Onozuka D, Sasaki S, Miyashita C, Yoshioka E, Yuasa M, Kishi R, Iida T, Uchi H, Furue M.	Concentrations of polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and polychlorinated biphenyls in blood and breast milk collected from pregnant women in Sapporo City, Japan.	Chemosphere.	85(11)	1694-1700	2011
Sasaki S, Braimoh TS, Yila TA, Yoshioka E, Kishi R	Self-reported tobacco smoke exposure and plasma cotinine levels during pregnancy - A validation study in Northern Japan.	Sci Total Environ.	412-413	114-118	2011
Kishi R, Sasaki S, Yoshioka E, Yuasa M, Sata F, Saijo Y, Kurahashi N, Tamaki J, Endo T, Sengoku K, Nonomura K, Minakami H.	Cohort Profile: The Hokkaido Study on Environment and Children's Health in Japan.	Int J Epidemiol.	40(3)	611-618	2011
Miyashita C, Sasaki S, SaijoY, Washino N, Okada E, Kobayashi S, Konishi K, Kajiwara J, Todaka T, Kishi R.	Effects of prenatal exposure to dioxin-like compounds on allergies and infections during infancy.	Environ Res.	111(4)	551-558	2011

厚生労働科学研究費補助金
化学物質リスク研究事業

前向きコーホート研究に基づく先天異常，免疫アレルギーおよび小児発達障害のリスク評価と環境化学物質に対する遺伝的感受性の解明

平成23年度　総括・分担研究報告書

別冊　【　研究成果の刊行物　】

研究代表者
北海道大学環境健康科学研究教育センター　岸　玲子

研究分担者
北海道大学大学院医学研究科生殖・発達医学講座産科・生殖医学分野　水上　尚典
札幌医科大学医学部産科周産期科・生殖内分泌科　遠藤　俊明
旭川医科大学医学部産婦人科学講座　千石　一雄
北海道大学大学院医学研究科外科治療学講座腎泌尿器外科学分野　野々村克也
北海道大学大学院医学研究科生殖・発達医学講座小児科学分野　有賀　正
福岡県保健環境研究所保健科学部生活化学課　梶原　淳睦
いであ株式会社環境創造研究所　松村　徹
北海道大学大学院獣医学研究科環境獣医科学講座毒性学分野　石塚真由美
北海道大学環境健康科学研究教育センター　安住　薫
北海道大学大学院医学研究科予防医学講座公衆衛生学分野　佐々木成子
旭川医科大学医学部健康科学講座地域保健疫学分野　吉岡　英治

平成24（2012）年3月

別冊【研究成果の刊行物】

目　次

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kanazawa A, Miyashita C, Okada E, Kobayashi S, Washino N, Sasaki S, Yoshioka E, Mizutani F, Chisaki Y, Saijo Y, Kishi R.	Blood persistent organochlorine pesticides of pregnant women relating to their characteristics in the Hokkaido Study on environment and children's health	Sci Total Environ			In press
池野多美子,小林澄貴,馬場俊明,岸玲子.	注意欠損/多動性障害(ADHD)に関する文献レビュー—有病率と発症の養育環境要因.	北海道公衆衛生学雑誌.			In press
Yila TA, Sasaki S, Miyashita C, Braimoh TS, Kashino I, Kobayashi S, Okada E, Baba T, Yoshioka E, Minakami H, Endo G, Sengoku K, Kishi R.	Effects of maternal 5,10-methylenetetrahydrofolate reductase C677T and A1298C polymorphisms and tobacco smoking on infant birth weight in a Japanese population.	J Epidemiology.			In press
那須民江,岸玲子.	胎生期低栄養と小児の健康.	日本衛生学雑誌.	67(1)	21	2012
Okada E, Sasaki S, Saijo Y, Washino N, Miyashita C, Kobayashi S, Konishi K, Ito YM, Ito R, Nakata A, Iwasaki Y, Saito K, Nakazawa H, Kishi R.	Prenatal exposure to perfluorinated chemicals and relationship with allergies and infectious diseases in infants.	Environ Res.	112(1)	118-125	2012

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
岸玲子	【地域における母子保健縦断調査の活用】 環境と子どもの健康に関する北海道コーホートの成果と今後の課題.	保健の科学	53(2)	98-104	2011
Todaka T, Hirakawa H, Kajiwara J, Onozuka D, Sasaki S, Miyashita C, Yoshioka E, Yuasa M, Kishi R, Iida T, Uchi H, Furue M.	Concentrations of polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and polychlorinated biphenyls in blood and breast milk collected from pregnant women in Sapporo City, Japan.	Chemosphere.	85(11)	1694-1700	2011
Sasaki S, Braimoh TS, Yila TA, Yoshioka E, Kishi R	Self-reported tobacco smoke exposure and plasma cotinine levels during pregnancy - A validation study in Northern Japan.	Sci Total Environ.	412-413	114-118	2011
Kishi R, Sasaki S, Yoshioka E, Yuasa M, Sata F, Saijo Y, Kurahashi N, Tamaki J, Endo T, Sengoku K, Nonomura K, Minakami H.	Cohort Profile: The Hokkaido Study on Environment and Children's Health in Japan.	Int J Epidemiol.	40(3)	611-618	2011
Miyashita C, Sasaki S, SaijoY, Washino N, Okada E, Kobayashi S, Konishi K, Kajiwara J, Todaka T, Kishi R.	Effects of prenatal exposure to dioxin-like compounds on allergies and infections during infancy.	Environ Res.	111(4)	551-558	2011

Science of the Total Environment 426 (2012) 73–82

Contents lists available at SciVerse ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Blood persistent organochlorine pesticides in pregnant women in relation to physical and environmental variables in The Hokkaido Study on Environment and Children's Health

Ayako Kanazawa [a], Chihiro Miyasita [a], Emiko Okada [b], Sumitaka Kobayashi [b], Noriaki Washino [b], Seiko Sasaki [b], Eiji Yoshioka [b], Futoshi Mizutani [c], Youichi Chisaki [c], Yasuaki Saijo [d], Reiko Kishi [a,*]

[a] Center for Environmental Health and Sciences, Hokkaido University, Kita 12, Nish 7, Kita-ku, Sapporo 060-0812, Japan
[b] Department of Public Health Sciences, Graduate School of Medicine, Hokkaido University, Kita 15, Nish 7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan
[c] IDEA Consultants, Inc., Riemon 1334-5, Yaizu, Shizuoka 421-0212, Japan
[d] Department of Health Science, Asahikawa Medical University, 1-1-1, Higashi 2-Jo, Midorigaoka, Asahikawa 078-8510, Hokkaido, Japan

ARTICLE INFO

Article history:
Received 3 October 2011
Received in revised form 24 February 2012
Accepted 27 February 2012
Available online 13 April 2012

Keywords:
Persistent organochlorine pesticides
Pregnant women
Whole blood
Age
Parity

ABSTRACT

The aim of this study was to document the exposure levels of pregnant women in Hokkaido to persistent organochlorine (POC) pesticides and the relationship between the body burdens of these pesticides and the study population's characteristics, such as age, pre-pregnancy body weight and calendar year in which blood was collected. From 2002 to 2005, whole blood samples were obtained from 186 pregnant women (aged 17 to 47 years) from the population of 514 women registered with the Sapporo Toho hospital cohort of the Hokkaido Study. Blood samples were analyzed by GC/NCIMS and GC/HRMS to quantify 29 POC pesticides. The subjects' demographic details were obtained from medical records and self-administered questionnaires. The Jonckheere–Terpstra test was used to determine relevant trends in the chemical concentrations of these pesticides and their relationship to the subjects' demographic details. Twenty-one of the 29 targeted compounds (including pesticides that have never been used in Japan, such as Mirex, Parlar-26 and Parlar-50) were detected in whole blood samples, and their log-transformed concentrations were found to significantly correlate with each other. The concentrations of *p,p′*-DDD, *o,p′*-DDE, *p,p′*-DDE, Parlar-26 and Parlar-50 declined from 2002 to 2005 ($p<0.05$). The pesticide concentrations appeared to have stronger associations with past conception than with parity, with most pesticide concentrations declining in a manner that appeared inversely related to past conceptions ($p<0.05$). Maternal age was positively associated with the following pesticide concentrations: *p,p′*-DDE, chlordanes group, *cis*-heptachlorepoxide, β-HCH and mirex. Maternal pre-pregnancy body weight was positively associated with the concentrations of dieldrin, HCB, β-HCH, Parlar-26 and Parlar-50, and appeared to be more strongly related to the body burdens of POC pesticides when compared with BMI associations. Further studies are required to evaluate the effects of POC pesticides on human health with regard to reproductive outcomes and child development.

1. Introduction

The use of most persistent organochlorine (POC) pesticides has been eliminated or restricted due to their persistence in the environment and their resulting bioaccumulation in humans and other animals. The lipophilic POCs are highly resistant to both abiotic and biotic degradation and appear to be transported long distances by weather systems (Bennett et al., 2001). The lipophilicity and long half-life of these chemicals, which are suspected endocrine disruptors (Routti et al., 2010; Elobeid et al., 2010), result in their distribution and accumulation on the body. In 2004, the Stockholm Convention on persistent organic pollutants (POPs) the production and usage of these compounds and encouraging environmental monitoring and awareness campaigns that focus on health concerns and ecosystems. At that time, the restricted compounds included nine POC pesticides, aldrin, chlordane, dieldrin, endrin, heptachlor, hexachlorobenzen, mirex, toxaphene and dichlorodiphenyltrichloroethane (DDT). In 2009, α-hexachlorocyclohexane (HCH), β-HCH and γ-HCH were added to the restricted list (http://chm.pops.int). Most POC pesticides were prohibited from being applied to Japanese agricultural fields in the 1970s, although heptachlor, dieldrin and chlordane were used

Abbreviations: BMI, body mass index; CI, confidence interval; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; GC, gas chromatography; GM, geometric mean; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; LOQ, limit of quantitation; NCI-MS, negative-ion chemical-ionization mass spectrometry; PCB, polychlorinated biphenyl; POC, persistent organochlorine; POPs, persistent organic pollutants; SCLV, solvent cut large volume; SD, standard deviation; SIM, selected ion monitoring analysis.

* Corresponding author. Tel.: +81 11 706 4747; fax: +81 11 706 4725.
E-mail address: rkishi@med.hokudai.ac.jp (R. Kishi).

0048-9697/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.scitotenv.2012.02.073

in termite control until the 1980s, despite being banned from agricultural applications. Although it was never registered for agricultural use, hexachlorobenzene (HCB) was used in industry until the 1980s. Mirex and toxaphene have never been produced or used in Japanese industry or agriculture (http://www.env.go.jp/chemi/prtr/risk0.html).

The body burdens of POC pesticides are known to be associated with reproductive outcomes (Cocco et al., 2005; Longnecker et al., 2001; Ribas-Fito et al., 2002; Siddiqui et al., 2003; Tan et al., 2009; Toft et al., 2010; Pathak et al., 2010, 2011), cognitive anomalies (Fernandez et al., 2007; Torres-Sanchez et al., 2008) and neurodevelopment (Eskenazi et al., 2006; Ribas-Fito et al., 2006; Torres-Sánchez, et al., 2009), although the adverse effects of POC pesticides on human health are only suspected. For the last few decades, the body burdens of these chemicals have been gradually decreasing (Konishi et al., 2001; Solomon and Weiss, 2002; Craan and Haines, 1998; Schade and Heinzow, 1998).

To better understand the physical effects of persistent POC pesticides, studies that monitor the exposure levels of humans, especially pregnant women, to POC pesticides should be conducted. In addition, because POCs are suspected to cross the placental barrier (Ando et al., 1985; Saxena et al., 1981), the relationship between POC exposure and the health outcomes of infants and children should be evaluated. We have previously reported associations between maternal exposure to chemicals, such as polychlorinated biphenyl (PCB), perfluorooctane sulfonate and perfluorooctanoate, and birth weight (Konishi, et al., 2009; Washino et al., 2009) as well as associations between maternal PCB exposure and infants' mental and motor development (Nakajima et al., 2006). The present study analyzes whole blood samples to determine the exposure levels of pregnant women to 29 POC pesticides and evaluates the associations between these chemical concentrations, the subjects' physical characteristics and environmental variables.

2. Materials and methods

2.1. Study population

From 2002 to 2005, 514 pregnant women registered with a hospital-based prospective cohort study entitled the "Hokkaido Study on Environment and Children's Health" (Kishi et al., 2011). The concentrations of POC pesticides were determined in 186 of the 374 whole blood samples obtained from this population. Data regarding the subjects' age, height, pre-pregnancy body weight, past conception(s), and parity were obtained from the subjects' medical records. Data regarding their levels of education, annual household incomes and smoking statuses during pregnancy were obtained through self-administered questionnaires.

All the subjects supplied their written informed consent, and this study was approved by the institutional ethical board for epidemiological studies at the Hokkaido University Graduate School of Medicine.

2.2. Exposure measurement

The 29 POC pesticides evaluated in this study were *o,p'*-DDT, *p,p'*-DDT; *o,p'*-dichlorodiphenyldichloroethylene (DDE), *p, p'*-DDE, *o,p'*-dichlorodiphenyldichloroethane (DDD), *p, p'*-DDD, *cis*-chlordane, *trans*-chlordane, *cis*-nonachlor, *trans*-nonachlor, oxychlordane, aldrin, dieldrin, endrin, heptachlor, *cis*-heptachlorepoxide, *trans*-heptachlorepoxide, HCB, α-HCH, β-HCH, γ-HCH, δ-HCH, mirex, Parlar-26, Parlar-41, Parlar-40, Parlar-44, Parlar-50, and Parlar-62. The internal standards (for the clean-up and syringe spikes) were ^{13}C-labeled isomers or d-isomers obtained from Cambridge Isotope Laboratory, Inc. (Andover, MA, USA). The organic solvents were of a grade appropriate for measurements of dioxins (Kanto Chemical Co. Inc., Tokyo; Wako Pure Chemicals, Osaka).

The concentrations of POC pesticides were measured according to the methods recommended by the Ministry of the Environment, as described below. All procedures were performed by IDEA Consultants, Inc. (Tokyo). Six milliliters of aqueous solution saturated with ammonium sulfate and 24 ml of 25% ethyl alcohol/hexane were added to 10 ml of whole blood with internal standards (for the clean-up spike) (0.1 ng each), and this mixture was shaken for 30 min. After the mixture was separated into two layers, the upper hexane layer was obtained as part of the extract solution. The procedure was then repeated with the lower layer and 20 ml hexane, and an additional upper hexane layer was obtained. The extract solution containing the combined hexane layers was washed with 20 ml of distilled water, dehydrated with sodium sulfate dehydrate, filtrated and concentrated to 10 ml under reduced pressure. This solution was then washed three times by shaking with 30 ml hexane-saturated acetonitrile to remove lipids. The resulting extract was washed with 3 ml distilled water, this mixture of organic and aqueous solvent was separated into two layers, and the upper hexane layer was removed. Next, 60 ml of distilled water was added to the acetonitrile extract, and the extraction procedure using 30 ml hexane was repeated twice. After washed with distilled water and dehydrated, the hexane extract was divided into two fractions (3:1, by volume): fraction 1 and fraction 2. Fraction 1 was purified using silica gel column chromatography (Wakogel C-200, Wako Pure Chemicals Industries; eluting solvent, 150 ml of hexane). Then internal standards (for syringe spikes) were added to fraction 1, and fraction 1 was injected into a gas chromatography/negative-ion chemical-ionization mass spectrometry (GC/NCI-MS) system for toxaphene measurement. Fraction 2 was purified using Florisil cartridge column chromatography (LC-Florisil, SUPELCO, Bellefonte, PA, USA; eluting solvent, 5% diethylether/hexane, 10 ml). Then, internal standards (for syringe spikes) were added to fraction 2, and fraction 2 was injected into a gas chromatography/high-resolution mass spectrometry (GC/HRMS) system for measurements of pesticides other than toxaphene.

For toxaphene measurements, a 6890 series GC system (Agilent Technologies, Ltd., Santa Clara, CA, USA) equipped with a DB-35ms column (i.d. 0.25 mm × 30 m, Agilent Technologies, Inc.) was connected to a mass spectrometer (BU20, JEOL Ltd., Tokyo). The injection was conducted in the splitless mode at 220 °C. The oven temperature was programmed as follows: 130 °C for 2 min, then a 15 °C/min increase up to 220 °C, a 2.5 °C/min increase up to 255 °C, a 10 °C/min increase up to 280 °C, and finally hold at 280 °C. The detector was operated in the NCI mode (interface temperature, 250 °C; ion source temperature, 180 °C; ionizing current, 300 μA; electron volt, 200 eV; acceleration volt, 2.5 kV). The target compounds' quantification and confirmation ions were as follows: Parlar-26, -40, -41 and -44, 378.8543, 376.8572; Parlar-50, 412.8153, 410.8182; Parlar-62, 376.8387, 374.8417.

Except for toxaphene, all pesticides were analyzed using an Agilent 6890 series GC connected to a mass spectrometer (AutoSpec-Ultima, Micromass Ltd., Manchester, UK). A BPX-Dioxin-I column (i.d. 0.15 mm × 30 m, Kanto Chemical Co. Inc.) was used for detection of chlordanes, drins and Heptachlor epoxide, while a RH-12ms column (i.d. 0.25 mm × 30 m, Inventx, Torrance, CA, USA) was used for detection of other pesticides. The injection was performed in Solvent Cut Large Volume (SCLV) mode, and the oven temperature was operated as follows: 160 °C for 1 min, then a 20 °C/min increase up to 300 °C, 300 °C for 8 min, a 70 °C/min decrease down to 160 °C, 160 °C for 1 min, a 4 °C/min increase up to 300 °C and finally hold at 300 °C. For the other pesticides, the injection was performed in splitless mode, and the oven temperature was programmed as follows: 130 °C for 1 min, then a 15°C/min increase up to 180 °C, a 4 °C/min increase up to 250 °C, a 15 °C/min increase up to 330 °C, and finally hold at 330 °C. The detector was operated in the selected ion monitoring analysis (SIM) mode using an interface temperature of 290 °C of interface temperature and an ion source temperature of 320 °C. The quantification and confirmation ions of the target compounds were as follows: HCH, 218.9116, 216.9145;

DDD, 235.0081, 237.0052; DDE, 246.0003, 247.9974; DDT, 235.0081, 237.0052; HCB, 283.8102, 285.8072; chlordane, 372.8260, 374.8230; nonachlor, 408.7840, 406.7870; oxychlordane, 386.8052, 388.8023; mirex, 271.8102, 273.8072; heptachlor, 271.8102, 273.8072; heptachlorepoxide, 352.8442, 354.8413; drins (aldrin, dieldrin and endrin), 262.8570, 264.8540.

The instrumental quantitation limit (IQL) was defined as 10 times the standard deviation (SD) of 7 measurements of the lowest standard concentration in the calibration curve(s). The limit of quantitation (LOQ) was calculated from the blood sample volume, the constant volume prior to injection and the injected volume.

2.3. Statistics

Age, pre-pregnancy body weight, height and pre-pregnancy body mass index (BMI) were divided into three categories using tertiles. Geometric means (GM) and 95% confidence intervals (CI) were calculated using GraphPad Prism 5 (San Diego, CA, USA). Regarding the 18 chemicals for which detection rates were above 50%, trends in each category's detected chemical concentrations were evaluated using the Jonckheere–Terpstra trend test in SPSS ver. 15 (SPSS, Inc., Chicago, Illinois). A value was considered significant when the p value was less than 0.05.

3. Results

The demographic characteristics of the subjects are given in Table 1. At the time of enrollment, the subjects' ages ranged from 17 to 47 years with a median of 31 years. The numbers of registered women from year-to-year were as follows: 2002, 35 (18.8%); 2003, 64 (34.4%); 2004, 78 (41.9%); 2005, 9 (4.8%). The subjects' heights ranged from 140 to 172 cm with a median of 158 cm, and their pre-pregnancy body weights ranged from 38 to 95 kg with a median of 52 kg. The subjects' pre-pregnancy BMI values ranged from 16.2 to 35.8 with a median of 20.6. The subjects' parity values ranged from 0 to 5 times with a mean (±SD) of 0.7±0.8 times. The subjects' past conceptions ranged from 0 to 6 times with a mean (±SD) of 1.3±1.3 times. Subjects with smoking histories accounted for 49.5% of the group, and those who smoked during pregnancy accounted for 11.8%. Blood was collected during pregnancy (24.1 to 40.7 gestational weeks, 67.2%) or after delivery (32.8%).

Table 2 presents the LOQ values, the detection rates (% of>LOQ) and the concentrations of 29 chemicals detected in whole blood samples. The detection rates of the DDTs were as follows: *o,p'*-DDT, 87.6%; *p,p'*-DDT, 100%; *o,p'*-DDD, 0.5%; *p,p'*-DDD, 66.7%; *o,p'*-DDE, 72.0%; and *p,p'*-DDE, 100%. In terms of median values (and range), the highest concentration detected among the DDTs was 610 (120–4600) pg/g wet mass of *p,p'*-DDE, and the second highest concentration was 23 (5.6–120) pg/g wet mass of *p,p'*-DDT. The detection rates of chlordanes were as follows: *cis*-chlordane, 98.9%; *trans*-chlordane, 54.8%; oxychlordane, 100%; *cis*-nonachlor, 100%; *trans*-nonachlor, 100%. Among the chlordanes, the highest concentration detected was 69 (14–510) pg/g wet mass of *trans*-nonachlor followed by 40 (7.9–250) pg/g wet mass of oxychlordane. With regard to the heptachlors, *cis*-heptachlorepoxide was detected in every sample, but heptachlor and *trans*-heptachlorepoxide were not detected. The detection rates of the drins group were as follows: aldrin, 0.5%; dieldrin, 100%; endrin, 0%. The dieldrin concentration was 18 (5.8–59) pg/g wet mass. The HCB detection rate was 100%, and the concentration of HCB was 100 (35–250) pg/g wet mass. The detection rates obtained for the HCH isomers were as follows: α-HCH, 8.1%; β-HCH, 100%; γ-HCH, 64.5%; δ-HCH, 0%. The detection rate of mirex was 98.9%, and the concentration of mirex was 6.0 (<2–30) pg/g wet mass. Regarding the toxaphene measurements, two chemicals were detected as follows: Parlar-26, 82.8% and Parlat-50, 85.5%. Parlar-40, Parlar-41, Parlar-44 and Parlar-62 were not detected. The concentrations of Parlar 26 and Parlar 50 were 5.2 (<3–19) and 7.6 (<4–27) pg/g wet mass, respectively.

Table 1
Characteristics of subjects.

Characteristics	N (%)	Median (range)	Mean±SD
Age (year)	186 (100%)	31 (17–47)	30.8±4.8
Height (cm)	186 (100%)	158 (140–172)	158.3±5.3
Pre-pregnancy body weight (kg)	186 (100%)	52 (38–95)	53.8±9.4
Pre-pregnancy BMI (kg/m^2)	186 (100%)	20.6 (16.2–35.8)	21.4±3.5
Educational level (year)			
9–12	79 (42.4%)	–	–
≥13	107 (57.6%)	–	–
Annual household income (million yen)			
<3	32 (17.2%)	–	–
3–5	86 (46.2%)	–	–
5–7	42 (22.6%)	–	–
≥7	26 (14.0%)	–	–
Parity (times)	186 (100%)	1 (0–5)	0.7±0.8
0	83 (44.6%)	–	–
1	81 (43.5%)	–	–
2	16 (8.6%)	–	–
3	5 (2.7%)	–	–
4	0 (0%)	–	–
5	1 (0.5%)	–	–
Past conception (times)	186 (100%)	1 (0–6)	1.3±1.3
0	52 (28.0%)	–	–
1	65 (34.9%)	–	–
2	41 (22.0%)	–	–
3–6	28 (15.1%)	–	–
History of smoking			
Yes	94 (49.5%)	–	–
No	92 (50.5%)	–	–
Smoking during pregnancy			
Yes	22 (11.8%)	–	–
No	164 (88.2%)	–	–
Blood sampling period:			
24.1–27.6 weeks of pregnancy	14 (7.5%)	–	–
30.0–40.7 weeks of pregnancy	111 (59.7%)	–	–
After delivery	61 (32.8%)	–	–
Year in which blood was collected			
2002	35 (18.8%)	–	–
2003	64 (34.4%)	–	–
2004	78 (41.9%)	–	–
2005	9 (4.8%)	–	–

Table 3 displays Pearson's correlation coefficient among the log-transformed concentrations of chemicals including '*p,p'*-DDT+*p,p'*-DDE', chlordanes (the sum of *cis*-chlordane, *trans*-chlordane, oxychlordane, *cis*-nonachlor and *trans*-nonachlor), *cis*-hepatachlorepoxide, dieldrin, HCB, β-HCH, mirex and 'Parlar 26+Parlar 50'. All correlations found among the chemicals were statistically significant, and most of the chemicals were well correlated with the others (r=0.49–0.77). HCB was strongly correlated with chlordanes (r=0.77). There were also strong correlations between β-HCH and '*p,p'*-DDT+*p,p'*-DDE' and between dieldrin and *cis*-heptachlorepoxide. On the other hand, the correlations between mirex and *cis*-heptachlorepoxide and between mirex and dieldrin were not strong (r=0.39 and 0.32). The correlations of mirex or 'Parlar 26+Parlar 50' with the other five pesticides are visualized as scatter plots in Fig. 1.

Table 4 presents the concentrations of 18 chemicals from blood collections separated into calendar years. The detection rates of tabulated pesticides were above 50%. The chemical concentrations were compared within three calendar year groups: 2002, 2003 and '2004+2005'. Statistical significances were observed for *p,p'*-DDD, *p,p'*-DDE, *o,p'*-DDE, '*p,p'*-DDE+*p,p'*-DDT', *trans*-chlordane, Parlar 26 and Parlar 50, and except for *p,p'*-DDD, each of these chemical's concentrations decreased as the calendar year increased.

Table 5 presents the concentrations of POC pesticides in relation to past conceptions. It appears that most of the chemicals' concentrations declined as the history of past conception(s) increased. In this regard,

Table 2
Limits of quantification (LOQ), detection rates (percents of > LOQ) and concentrations of persistent organochlorine pesticides in the whole blood of pregnant women.

Compounds	LOQ (pg/g of wet)	≥LOQ		Concentration (pg/g wet)	
		(n)	(%)	Median (range)	GM (95% CI)
DDTs					
o,p'-DDT	2	163	87.6	3.7 (<2–13)	3.4 (3.1–3.7)
p,p'-DDT	1	186	100	23 (5.6–120)	24 (22–26)
o,p'-DDD	1	1	0.5	<1 (<1–1.1)	0.50 (0.50–0.51)
p,p'-DDD	1	124	66.7	1.3 (<1–9.0)	1.2 (1.1–1.4)
o,p'-DDE	1	134	72.0	1.4 (<1–6.2)	1.2 (1.1–1.3)
p,p'-DDE	2	186	100	610 (120–4600)	610 (560–670)
Chlordanes					
cis-Chlordane	0.8	184	98.9	2.1 (<0.8–18)	2.1 (2.0–2.3)
trans-Chlordane	0.6	102	54.8	0.60 (<0.6–3.8)	0.60 (0.54–0.66)
Oxychlordane	2	186	100	40 (7.9–250)	41 (38–44)
cis-Nonachlor	0.8	186	100	10 (1.6–38)	10 (9.5–11)
trans-Nanachlor	0.6	186	100	69 (14–510)	72 (66–77)
Heptachlors					
Heptachlor	2	0	0	–	–
cis-Heptachlorepoxide	2	186	100	28 (7.1–200)	28 (26–30)
trans-Heptachlorepoxide	0.9	0	0	–	–
Drins					
Aldrin	0.7	1	0.5	<0.7 (<0.7–13)	0.36 (0.34–0.37)
Dieldrin	0.9	186	100	18 (5.8–59)	18 (17–19)
Endrin	2	0	0	–	–
HCB	2	186	100	100 (35–250)	100 (97–110)
HCH isomers					
α-HCH	2	15	8.1	<1 (<1–3.9)	1.1 (1.0–1.1)
β-HCH	2	186	100	150 (20–1200)	150 (140–170)
γ-HCH	1	120	64.5	1.3 (<1–100)	1.2 (1.1–1.3)
δ-HCH	2	0	0	–	–
Mirex	2	184	98.9	6.0 (<2–30)	6.2 (5.7–6.7)
Toxaphene					
Parlar 26	3	154	82.8	5.2 (<3–19)	4.7 (4.3–5.2)
Parlar 40	2	0	0	–	–
Parlar 41	3	0	0	–	–
Parlar 44	3	0	0	–	–
Parlar 50	4	159	85.5	7.6 (<4–27)	7.0 (6.4–7.7)
Parlar 62	20	0	0	–	–

statistically significant results were obtained for *p,p'*-DDT, *o,p'*-DDE, *cis*-chlordane, oxychlordane, *cis*-nonachlor, *trans*-nonachlor, *cis*-heptachlorepoxide, HCB, β-HCH, mirex, Parlar 26 and Parlar 50.

Table 6 presents the concentrations of POC pesticides in relation to parity. Similar to the correlation observed with regard to past conceptions, the concentrations of most chemicals appeared to decline with increased parity. In this regard, statistically significant results were obtained for measurements of *cis*-chlordane, oxychlordane, *cis*-nonachlor, *trans*-nonachlor, HCB, β-HCH, Parlar 26 and Parlar 50.

Table 7 presents the concentrations of POC pesticides in relation to age. The chemical concentrations detected were compared with regard to three categories (divided into tertiles), and statistically significant age relationships were observed for *p,p'*-DDE, '*p,p'*-DDE + *p,p'*-DDT', *cis*-chlordane, oxychlordane, *cis*-nonachlor, *trans*-nonachlor, *cis*-heptachlorepoxide, HCB, β-HCH, mirex and Parlar 50. It appears that these concentrations increased with maternal age.

Table 8 presents the concentrations of POC pesticides in relation to pre-pregnancy body weight. The chemical concentrations were compared with regard to three categories (divided into tertiles), and statistically significant relationships were observed for *o,p'*-DDT, *p,p'*-DDT, *o,p'*-DDE, dieldrin, β-HCH, Parlar-26 and Parlar-50.

Table 9 presents the concentrations of POC pesticides in relation to pre-pregnancy BMI. The concentrations of dieldrin, Parlar 26 and Parlar 50 significantly increased when BMI increased; however, the concentration of mirex significantly declined with an increase in BMI.

4. Discussion

Studies employing whole blood samples may have an advantage in that the influence of dietary lipids is less in whole blood than in serum or plasma. Although it has been found that POC pesticide concentrations are higher in sea-turtle plasma than in whole blood (Keller

Table 3
Correlation among log-transformed concentrations of major compounds[a].

	p,p'-DDT + *p,p'*-DDE	Chlordanes	*cis*-Heptachlor epoxide	Dieldrin	HCB	β-HCH	Mirex	Parlar 26 + Parlar 50
p,p'-DDT + *p,p'*-DDE	1	–	–	–	–	–	–	–
Chlordanes[b]	0.61*	1	–	–	–	–	–	–
cis-Heptachlorepoxide	0.54*	0.62*	1	–	–	–	–	–
Dieldrin	0.47*	0.53*	0.73*	1	–	–	–	–
HCB	0.67*	0.77*	0.64*	0.56*	1	–	–	–
β-HCH	0.72*	0.69*	0.56*	0.49*	0.77*	1	–	–
Mirex	0.54*	0.72*	0.39*	0.32*	0.61*	0.50*	1	–
Parlar 26 + Parlar 50	0.54*	0.63*	0.56*	0.63*	0.68*	0.53*	0.57*	1

[a] Log-transformed concentrations of chemicals were tested with Pearson's correlation test after < LOQ was substituted with the value of LOQ/2.
[b] Chlordanes = *cis*-chlordane + *trans*-chlordane + oxychlordane + *cis*-nonachlor + *trans*-nonachlor.
* $P<0.01$.

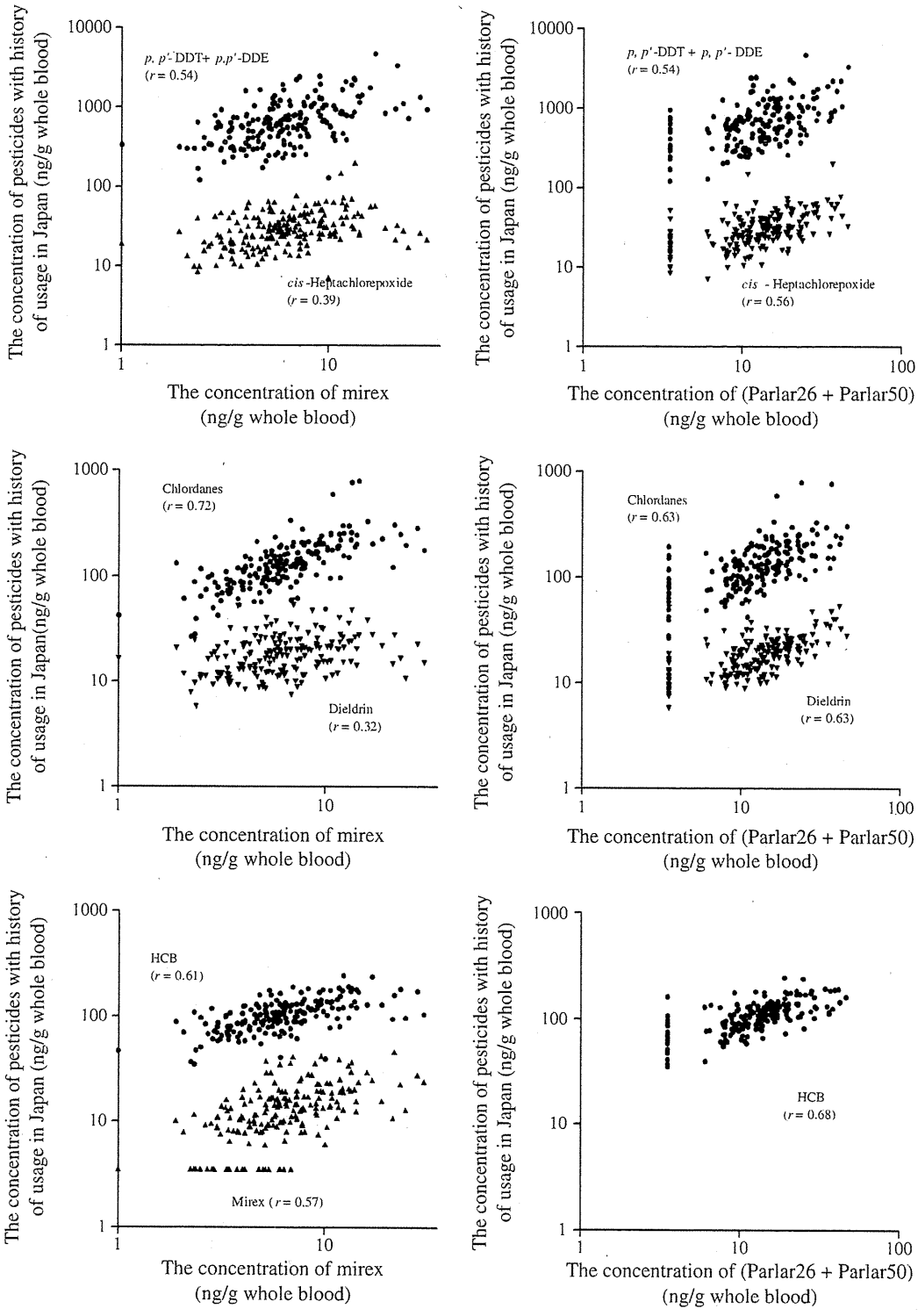

Fig. 1. Scatter plots of POC pesticide concentrations. Left row, mirex vs. others; right row, (Parlar 26 + Parlar 50) vs. others.

et al., 2004), published research regarding the presence of POC pesticides in whole blood samples has been limited (Iwasaki et al., 2008; Fukata et al., 2005; Sasaki et al., 1991; Ostrea et al., 2009; Sugiura-Ogasawara et al., 2003). Thus, comparisons of the present study with previous studies are necessarily limited, because most previously published studies involve POC pesticide concentrations detected in serum or plasma. Two previously published Japanese studies (Fukata et al., 2005; Sugiura-Ogasawara et al., 2003), which involved approximately the same time period as that employed in the present study, have reported POC pesticide concentrations that compare favorably to those reported herein. The concentrations of POC pesticides in the present study were similar to those in the previous studies. We have suggested that exposure levels are low in Japan, as indicated by reports of lower POC pesticide contamination levels in milk in Japan than in

Table 4
Concentrations of organochlorine pesticides in relation to year in which blood was collected (pg/g wet mass).

Compounds	2002 (n = 35)		2003 (n = 64)		2004–2005 (n = 87)		P value[a]
	Med (range)	GM (95% CI)	Med (range)	GM (95% CI)	Med (range)	GM (95% CI)	
DDTs							
o,p′-DDT	4.0 (<2.0–13)	4.1 (3.3–5.0)	3.7 (<2.0–9.7)	3.4 (2.9–3.9)	3.4 (<2.0–11)	3.2 (2.8–3.6)	0.06
p,p′-DDT	25 (11–120)	27 (22–33)	22 (10–100)	25 (21–28)	22 (5.6–73)	23 (20–25)	0.32
p,p′-DDD	<1.0 (<1.0–4.3)	0.85 (0.67–1.1)	1.3 (<1.0–6.1)	1.1 (0.93–1.3)	1.7 (<1.0–9.0)	1.6 (1.3–1.8)	<0.01
o,p′-DDE	1.7 (<1.0–6.2)	1.6 (1.3–2.1)	1.3 (<1.0–4.6)	1.2 (1.0–1.4)	1.3 (<1.0–4.4)	1.1 (1.0–1.3)	<0.02
p,p′-DDE	680 (250–4600)	730 (570–940)	660 (160–2400)	640 (550–750)	540 (120–2400)	550 (480–620)	0.04
p,p′-DDE + *p,p′*-DDT	690 (270–4700)	760 (590–970)	690 (170–2400)	670 (580–780)	560 (120–2500)	570 (500–650)	0.045
Chlordanes							
cis-Chlordane	1.8 (1.2–18)	2.2 (1.8–2.8)	2.1 (0.83–5.8)	2.1 (1.8–2.3)	2.1 (<0.80–17)	2.2 (1.9–2.4)	0.57
trans-Chlordane	<0.60 (<0.60–1.7)	0.3 (0.3–0.4)	0.63 (<0.60–3.8)	0.59 (0.51–0.69)	0.8 (<0.60–2.9)	0.74 (0.64–0.86)	<0.01
Oxychlordane	37 (18–200)	41 (34–50)	40 (11–110)	40 (36–46)	43 (7.9–250)	40 (36–45)	0.46
cis-Nonachlor	8.9 (4.7–38)	11 (8.8–13)	10 (3.2–26)	9.9 (8.7–11)	11 (1.6–34)	10 (9.2–12)	0.43
trans-Nonachlor	60 (37–510)	73 (59–91)	67 (25–170)	69 (61–77)	80 (14–490)	73 (65–83)	0.21
cis-Heptachlorepoxide	29 (11–200)	31 (26–37)	28 (9.9–78)	28 (24–31)	28 (7.1–150)	28 (25–31)	0.46
Dieldrin	22 (9.5–53)	21 (18–24)	17 (8.9–54)	17 (15–19)	17 (5.8–59)	17 (16–19)	0.08
HCB	100 (61–240)	100 (94–120)	110 (58–190)	110 (98–120)	100 (35–250)	98 (90–110)	0.47
HCHs							
β-HCH	154 (58–770)	170 (140–200)	160 (32–640)	170 (140–190)	140 (20–1200)	140 (120–160)	0.13
γ-HCH	1.0 (<1.0–6.7)	0.97 (0.74–1.3)	1.3 (<1.0–100)	1.3 (0.99–1.6)	1.3 (<1.0–6.6)	1.2 (1.1–1.4)	0.12
Mirex	6.0 (2.3–30)	6.4 (5.2–7.9)	5.6 (2.5–24)	6.1 (5.4–6.9)	6.2 (<2.0–28)	6.2 (5.5–7.0)	0.70
Parlar 26	5.6 (<3.0–19)	5.9 (4.7–7.3)	5.1 (<3.0–18)	4.8 (4.0–5.7)	5.0 (<3.0–13)	4.3 (3.8–5.0)	0.046
Parlar 50	8.8. (<4.0–27)	8.9 (7.2–11)	7.8 (<4.0–24)	7.4 (6.2–8.8)	6.4 (<4.0–23)	6.1 (5.3–7.0)	<0.01

[a] *P* values resulted from two-tailed Jonckheere–Terpstra trend test.

China, Hong Kong, and Vietnam (Haraguchi et al., 2009; Solomon and Weiss, 2002).

Compared to the results of this study, high body-burden levels of POC pesticides were reported in the 1960s and 1970s. In a 1960s survey of 339 pregnant women in the USA, *p,p′*-DDT and *p,p′*-DDE were detected at levels of 15.0 ± 8.8 and 53.9 ± 35.3 ppb (pg/g serum), respectively (James et al., 2002). In a 1979 survey, the mean serum DDT concentration of 499 samples (men and women) detected (159.4 ng/ml) was 10 times the US geometric mean (15 ng/ml serum) (Kress et al., 1981). In the 1970s in Japan, 7.5 ± 7.0 ppb of *p,p′*-DDT and 15.7 ± 9.3 ppb of *p,p′*-DDE were detected in plasma samples from 86 women (Yamaguchi et al., 1975). After POC pesticides were banned, the body burdens of these chemicals remained at peak concentrations throughout the 1960s and 1970s and then decreased over several decades (Craan and Haines, 1998; Dallaire et al., 2002; Lackmann, 2005; Konishi et al., 2001; Solomon and Weiss, 2002). In contrast, the concentrations of related metabolites, such as DDE and oxychlordane, increased over this time period, resulting in higher bodily concentrations of metabolites versus their precursors. As presented in Table 2, the concentrations of metabolites, such as *p,p′*-DDE, oxychlordane and *cis*-heptachlorepoxide, determined in this study were higher than their precursors, such as *p,p′*-DDT, *cis*-chlordane, *trans*-chlordane, *cis*-heptachlor and *trans*-heptachlor. The ratios of DDE to DDT obtained in this and other recent studies (Fukata et al., 2005; Wittsiepe et al., 2008) are higher than those reported in the 1960s and 1970s (James et al., 2002; Yamaguchi et al., 1975).

Lackmann (2005) reported a decline in neonatal serum *p,p′*-DDE concentrations in Germany, obtaining a highest mean value of 1.49 ng/ml in 1984–1985 and a lowest mean value of 0.18 ng/ml in 2002. According to Dallaire et al. (2002), the mean cord blood concentrations of chlordanes, DDTs and HCB considerably declined in Canada from 1993 to 2000. In their analysis of 392 blood samples collected from 1993 to 2007 in Sweden, Hardell et al. (2010) observed approximately 10% reductions by year in the concentrations of PCBs, HCB, DDE and chlordanes. As presented in Table 4, most of the chemicals analyzed in the present study were also found to decrease from year to year, consistent with reports of their decreasing concentrations in milk in recent decades. Konishi et al. (2001) reported that the concentrations of contaminants in milk decreased from 1972 to 1998 in Osaka city, Japan. For instance, the concentrations of β-HCH and DDT declined to less than 3% of their peak levels by the mid-1970s. In Sweden, after peaking in the mid 1970s, the concentrations of dieldrin, β-HCH and DDT in human milk dramatically decreased throughout the 1980s and 1990s (Solomon and Weiss, 2002). In Canada, after peaking in the 1960s and 1970s, the concentrations of most POC contaminants in milk decreased, and the concentration of β-HCH decreased after peaking in the 1980s (Craan and Haines, 1998). In Northern Germany, the concentrations of DDT, HCB and β-HCH in milk declined by 10–20% over the decade from 1986 to 1997 (Schade and Heinzow, 1998). Thus, more recent reductions in the body burdens of POC pesticides appear to be a global trend.

Based on the samples collected from 1979 elderly Canadian in 2003, Medehouenou et al. (2011) reported that the lipid-adjusted POC concentrations of *p,p′*-DDTs, Chlordanes, β-HCH and HCB strongly correlated with one another. The present study, which used samples collected from 2002 to 2005, also revealed strong correlations among the concentrations of eight POC pesticides (Table 3). The correlations between *p,p′*-DDTs and chlordanes and between β-HCH and HCB found within our study appear to be stronger than those reported in the Canadian study, of which sampling area involved the 36 urban and surrounding areas. The narrow sampling area used in our study, which was conducted using a single hospital-based population may have contributed to the higher correlation coefficients obtained.

Notably, mirex, Parlar-26 and Parlar-50, which have never been used in Japan, were detected in most samples (>LOQ%, 82.8% and 85.5%), and the log-transformed concentrations of these compounds were positively correlated with other pesticides used in the past ($p<0.01$). According to a public announcement of the Ministry of the Environment, mirex, Parlar-26 and Parlar-50 were not found in environmental samples in the 1983 survey; however, these chemicals were detected in the atmosphere, solid surface sediments, shellfish, fish and seabirds in 2003 (Ministry of the Environment, 2005, 2006). It is possible that, in the past, mirex pollution may have resulted from imported products containing mirex as a flame retardant. The Japanese environment may also be influenced by the usage of pesticides in neighboring countries. For example, China produced toxaphene from 1964 to 1980, though this chemical was banned for all purposes in 1987 (Wong et al., 2005). Given that persistent organic pollutants are known

Table 5
Concentrations of organochlorine pesticides in relation to past conceptions (pg/g wet mass).

Compounds	None (n = 52)		1 time (n = 65)		2 times (n = 41)		3–6 times (n = 28)		P value[a]
	Med (range)	GM (95% CI)	Med (range)	GM (95% CI)	Med (range)	GM (95% CI)	Med (range)	GM (95%CI)	
DDTs									
o,p′-DDT	3.6 (<2.0–13)	3.5 (2.9–4.1)	3.9 (<2.0–9.1)	3.7 (3.3–4.3)	3.5 (<2.0–11)	3.2 (2.6–3.9)	3.1 (<2.0–6.8)	2.8 (2.2–3.5)	0.15
p,p′-DDT	28 (<9.9–120)	27 (23–31)	25 (8.1–73)	26 (23–29)	20 (6.8–66)	21 (18–25)	22 (5.6–100)	21 (16–26)	0.03
p,p′-DDD	1.3 (<1.0–9.0)	1.4 (1.1–1.7)	1.3 (<1.0–6.1)	1.2 (1.0–1.5)	1.4 (<1.0–4.9)	1.2 (0.94–1.5)	1.3 (<1.0–5.5)	1.1 (0.84–1.5)	0.31
o,p′-DDE	1.4 (<1.0–6.2)	1.4 (1.1–1.6)	1.4 (<1.0–4.6)	1.3 (1.1–1.5)	1.3 (<1.0–3.4)	1.1 (0.91–1.3)	1.1 (<1.0–2.2)	1.0 (0.82–1.2)	0.02
p,p′-DDE	690 (160–4600)	680 (560–810)	670 (120–2400)	650 (550–760)	540 (220–1900)	550 (450–660)	550 (120–2100)	520 (400–670)	0.07
p,p′-DDE + *p,p′*-DDT	710 (170–4700)	710 (590–850)	690 (130–2400)	670 (580–790)	560 (230–1900)	570 (470–690)	570 (120–2200)	540 (420–700)	0.07
Chlordanes									
cis-Chlordane	2.4 (<0.80–18)	2.4 (2.1–2.9)	2.1 (0.84–17)	2.2 (1.9–2.5)	2.0 (0.83–5.8)	2.0 (1.7–2.3)	1.8 (0.8–3.9)	1.7 (1.5–2.1)	<0.01
trans-Chlordane	0.61 (<0.60–2.5)	0.56 (0.46–0.68)	0.65 (<0.60–2.9)	0.61 (0.51–0.72)	0.66 (<0.60–3.8)	0.63 (0.50–0.78)	0.63 (<0.60–2.0)	0.60 (0.45–0.74)	0.66
Oxychlordane	45 (19–200)	48 (42–55)	43 (7.9–250)	42 (37–49)	38 (9.4–94)	35 (30–41)	34 (14–88)	34 (28–40)	<0.01
cis-Nonachlor	12 (5.3–38)	12 (11–14)	10 (2.0–34)	11 (9.3–12)	9.3 (1.6–26)	8.8 (7.4–10)	9.4 (2.4–28)	8.5 (6.7–11)	<0.01
trans-Nonachlor	79 (33–510)	84 (72–98)	71 (17–490)	73 (64–84)	60 (14–170)	63 (53–74)	58 (21–220)	61 (50–75)	<0.01
cis-Heptachlorepoxide	30 (11–200)	31 (27–36)	31 (7.1–64)	29 (25–32)	24 (9.9–150)	26 (22–31)	24 (9.8–78)	25 (20–31)	0.02
Dieldrin	20 (8.8–53)	19 (17–21)	17 (8.4–47)	17 (16–19)	16 (7.5–59)	17 (15–19)	19 (5.8–54)	17 (14–21)	0.21
HCB	120 (65–240)	110 (110–120)	100 (35–250)	110 (96–110)	90 (37–190)	90 (79–100)	91 (47–190)	91 (80–110)	<0.01
HCHs									
β-HCH	170 (38–770)	170 (150–200)	150 (20–640)	150 (130–180)	120 (32–1200)	130 (100–160)	140 (34–600)	140 (110–190)	0.049
γ-HCH	1.3 (<1.0–7.2)	1.2 (0.96–1.5)	1.3 (<1.0–100)	1.3 (1.0–1.6)	1.3 (<1.0–4.8)	1.3 (1.0–1.6)	0.78 (<1.0–3.0)	0.89 (0.70–1.1)	0.40
Mirex	6.5 (2.3–30)	6.9 (5.9–8.1)	6.5 (2.1–28)	6.6 (5.8–7.5)	5.6 (<2.0–23)	5.3 (4.5–6.3)	5.1 (1.9–21)	5.5 (4.4–6.9)	0.02
Parlar 26	6.0 (<3.0–19)	5.9 (5.0–7.0)	5.2 (<3.0–17)	5.0 (4.3–5.8)	4.1 (<3.0–19)	3.9 (3.1–4.8)	4.0 (<3.0–18)	3.8 (2.9–5.0)	<0.01
Parlar 50	9.3 (<4.0–27)	8.6 (7.2–10)	7.9 (<4.0–22)	7.5 (6.5–8.7)	6.2 (<4.0–23)	5.8 (4.7–7.2)	6.0 (<4.0–24)	5.3 (4.0–7.1)	<0.01

[a] *P* values resulted from two-tailed Jonckheere–Terpstra trend test.

to diffuse a great-distance from their source(s), *trans*-border environmental pollution is certainly possible.

Associations between the POC pesticide concentrations found in blood samples and the corresponding subjects' characteristics are described below.

Hardell et al. (2010) reported that there was the association between parity and the PCB blood concentrations, although there were not significant associations between parity and the concentrations of HCB, DDE and chlordanes. Cao et al. (2011) reported an association between parity and the serum concentrations of HCB, β-HCH and *p,p′*-DDE in 1483 samples collected from 2008 to 2009 in Shanghai. In the present study, the concentrations of most chemicals decreased with past conceptions and/or with parity and exhibited a stronger association with past conceptions than with parity.

The concentrations of most chemicals increased with the age of the subject (Table 7), consistent with a longer exposure period for older subject groups. Environmental pollutant levels and exposure levels should also be higher for subjects born during time periods that enabled greater exposure(s). In addition, associations between chemical concentrations appear more strongly associated with pre-pregnancy body weight(s) than with BMI (Tables 6 and 7). Pre-pregnancy body weight may be better than BMI, as a surrogate for a body pool size of lipophilic pollutants. There were no significant trends in the concentrations of most chemicals in relation to subjects' heights; however, there was a statistically significant effect of height on the concentration of *trans*-chlordane alone (determined by the Jonckheere–Terpstra trend test, data not shown). No significant associations were found between most of the measured chemical concentrations and the subjects' educational levels (9–12 years, ≥13 years), smoking during pregnancy or annual household incomes (<5 million yen and ≥5 million yen; determined by Mann–Whitney *U* test, data not shown). However, a significant association was found between detected mirex concentrations and smoking histories (determined by Mann–Whitney *U* test, data not shown; $p<0.05$ determined by Jonckheere–Terpstra trend test, data not shown). Samples grouped according to their collections in the 2nd trimester, 3 rd trimester and after delivery revealed a significant association among the concentrations of *p,p′*-DDD, *trans*-chlordane and mirex and the natal stage during which blood was collected (determined by Jonckheere–Terpstra trend test, data not shown).

Cao et al. (2011) have reported a positive association between age, pre-pregnancy weight and BMI with serum concentrations of *p,p′*-DDE and β-HCH. Their findings regarding the association of age and the concentrations of *p,p′*-DDE and β-HCH are consistent with our results. In addition, based on a study that age-matched 1055 healthy controls to breast cancer subjects in France, Bachelet et al. (2011) have reported a positive association between age and detected *p,p′*-DDE concentrations. Carrizo et al. (2006) have reported a positive correlation between POC contamination levels in cord blood and maternal age, indicating that fetal exposure levels are higher in older mothers than in younger mothers. Similarly, Wittsiepe et al. (2008) have shown that HCB levels increase significantly with age. In their survey of 53 men, Hue et al. (2007) have demonstrated a positive correlation between age and total POC concentrations in plasma (including PCB and several pesticides) and determined that there is no association between BMI an total POC concentrations in plasma. Schildkraut et al. (1999) have demonstrated a positive correlation between BMI and serum DDE concentration, and Modehouenou et al. (2011) have reported that age (65 to 85 over) and BMI are positively associated with β-HCH, HCB, *trans*-nonachlor and *p,p′*-DDE concentrations.

The present study involves persistent POC pesticide measurements in whole-blood samples from pregnant women in Hokkaido. We have detected 21 chemicals, including three chemicals with no history of use in Japan that may have been distributed through long-distance transport mechanisms. This study suggests that contamination levels of POC pesticides are low compared to previous studies and that exposure levels are decreasing with each passing year. We have evaluated

Table 6
Concentrations of organochlorine pesticides in relation to parity (pg/g wet mass).

Compounds	None (n = 83)		1 time (n = 81)		2–5 times (n = 22)		P value[a]
	Med (range)	GM (95% CI)	Med (range)	GM (95% CI)	Med (range)	GM (95% CI)	
DDTs							
o,p′-DDT	3.6 (<2.0–13)	3.5 (3.1–4.0)	3.8 (<2.0–11)	3.3 (2.9–3.9)	3.5 (<2.0–7.3)	3.1 (2.4–3.9)	0.66
p,p′-DDT	25 (6.8–120)	25 (23–28)	22 (5.6–70)	23 (21–26)	20 (7.1–100)	22 (17–29)	0.27
p,p′-DDD	1.3 (<1.0–9.0)	1.3 (1.1–1.5)	1.5 (<1.0–6.1)	1.3 (1.1–1.5)	<1.0 (<1.0–5.5)	1.1 (0.71–1.6)	0.65
o,p′-DDE	1.4 (<1.0–6.2)	1.4 (1.2–1.6)	1.3 (<1.0–4.6)	1.1 (1.0–1.3)	1.2 (<1.0–2.2)	1.0 (0.78–1.3)	0.07
p,p′-DDE	670 (160–4600)	670 (580–760)	630 (120–2400)	590 (510–680)	530 (190–2100)	490 (370–660)	0.07
p,p′-DDE + *p,p′*-DDT	700 (170–4700)	690 (610–790)	640 (120–2400)	620 (530–710)	560 (200–2200)	520 (390–690)	0.07
Chlordanes							
cis-Chlordane	2.4 (<0.80–18)	2.4 (2.1–2.7)	2.0 (0.80–5.9)	2.0 (1.8–2.3)	1.7 (0.83–4.7)	1.8 (1.5–2.2)	0.01
trans-Chlordane	0.61 (<0.60–2.5)	0.56 (0.48–0.64)	0.67 (<0.60–3.8)	0.66 (0.57–0.78)	<0.60 (<0.60–2.0)	0.51 (0.38–0.68)	0.60
Oxychlordane	46 (19–250)	48 (43–54)	39 (7.9–110)	37 (33–41)	28 (9.4–88)	29 (22–38)	<0.01
cis-Nonachlor	12 (3.7–38)	12 (11–13)	9.4 (2.0–28)	9.5 (8.4–11)	8.0 (1.6–28)	8.0 (6.0–11)	<0.01
trans-Nonachlor	83 (33–510)	83 (74–94)	66 (17–170)	66 (59–73)	52 (14–220)	57 (42–76)	<0.01
cis-Heptachlorepoxide	30 (9.9–200)	30 (27–33)	28 (7.1–150)	28 (25–32)	22 (9.9–78)	24 (18–31)	0.07
Dieldrin	20 (8.6–59)	19 (17–20)	17 (5.8–47)	17 (16–19)	15 (7.8–54)	16 (13–20)	0.19
HCB	120 (63–250)	110 (110–120)	97 (35–190)	98 (91–110)	74 (37–190)	78 (65–94)	<0.01
HCHs							
β-HCH	170 (38–770)	180 (160–200)	150 (20–600)	140 (120–160)	110 (32–1200)	120 (81–180)	<0.01
γ-HCH	1.3 (<1.0–7.2)	1.2 (1.0–1.4)	1.2 (<1.0–100)	1.3 (1.0–1.5)	1.1 (<1.0–3.2)	0.98 (0.75–1.3)	0.60
Mirex	6.5 (1.9–30)	6.7 (5.9–7.5)	6.0 (<2.0–28)	6.0 (5.3–6.7)	5.2 (2.3–21)	5.4 (4.2–6.9)	0.08
Parlar 26	5.7 (<3.0–19)	5.5 (4.8–6.3)	4.4 (<3.0–19)	4.4 (3.8–5.1)	4.0 (<3.0–18)	3.6 (2.7–4.9)	<0.01
Parlar 50	8.6 (<4.0–27)	8.1 (7.1–9.2)	6.6 (<4.0–23)	6.6 (5.6–7.6)	6.0 (<4.0–24)	5.2 (3.9–7.1)	<0.01

[a] *P* values resulted from two-tailed Jonckheere–Terpstra trend test.

Table 7
Concentrations of organochlorine pesticides in relation to age (pg/g wet mass).

Compounds	T1: ≤29 years (n = 77)		T2: 30–33 years (n = 55)		T3: ≥34 years (n = 54)		P value[a]
	Med (range)	GM (95% CI)	Med (range)	GM (95% CI)	Med (range)	GM (95% CI)	
DDTs							
o,p′-DDT	3.4 (<2.0–11)	3.2 (2.8–3.7)	3.8 (<2.0–13)	3.6 (3.1–4.2)	3.9 (<2.0–9.1)	3.4 (2.8–4.0)	0.32
p,p′-DDT	21 (5.6–120)	22 (19–25)	26 (9.9–73)	26 (23–30)	27 (6.8–100)	25 (21–30)	0.06
p,p′-DDD	1.2 (<1.0–7.2)	1.1 (0.90–1.3)	1.7 (<1.0–6.1)	1.4 (1.2–1.7)	1.3 (<1.0–9.0)	1.3 (1.1–1.6)	0.09
o,p′-DDE	1.3 (<1.0–5.7)	1.1 (0.98–1.3)	1.4 (<1.0–6.2)	1.4 (1.2–1.6)	1.4 (<1.0–4.6)	1.2 (1.0–1.5)	0.22
p,p′-DDE	510 (120–4600)	500 (430–570)	720 (190–2400)	710 (610–820)	760 (120–2400)	700 (580–860)	<0.01
p,p′-DDE + *p,p′*-DDT	540 (120–4700)	520 (450–600)	740 (200–2400)	740 (640–860)	800 (130–2500)	730 (600–890)	<0.01
Chlordanes							
cis-Chlordane	1.9 (0.84–18)	2.0 (1.7–2.2)	2.1 (<0.80–17)	2.2 (1.9–2.6)	2.5 (0.83–8.0)	2.4 (2.0–2.8)	0.02
trans-Chlordane	0.66 (<0.60–3.8)	0.62 (0.53–0.72)	0.65 (<0.60–2.5)	0.64 (0.53–0.76)	<0.60 (<0.60–2.9)	0.52 (0.43–0.63)	0.18
Oxychlordane	37 (7.9–200)	35 (31–40)	44 (16–250)	44 (38–50)	49 (9.4–170)	46 (40–53)	<0.01
cis-Nonachlor	9.1 (2.0–38)	9.0 (7.9–10)	10 (4.5–34)	11 (9.7–13)	11 (1.6–33)	11 (9.8–13)	<0.01
trans-Nonachlor	60 (17–510)	63 (55–71)	69 (32–490)	76 (66–87)	87 (14–380)	82 (71–95)	<0.01
cis-Heptachlorepoxide	26 (8.4–200)	25 (22–28)	30 (12–150)	31 (27–35)	28 (7.1–78)	30 (26–35)	0.02
Dieldrin	17 (5.8–59)	17 (15–19)	20 (8.8–39)	19 (17–20)	17 (7.8–54)	18 (16–20)	0.38
HCB	97 (35–250)	96 (88–100)	110 (55–180)	110 (100–120)	110 (37–190)	100 (93–120)	0.045
HCHs							
β-HCH	120 (20–770)	110 (97–130)	170 (47–400)	170 (150–190)	210 (30–1200)	200 (170–250)	<0.01
γ-HCH	1.2 (<1.0–7.2)	1.1 (0.92–1.3)	1.3 (<1.0–100)	1.4 (1.1–1.8)	1.2 (<1.0–6.6)	1.2 (0.94–1.4)	0.59
Mirex	4.8 (<2.0–22)	4.8 (4.2–5.4)	6.5 (3.1–16)	6.8 (6.1–7.5)	8.6 (2.3–30)	8.2 (7.0–9.6)	<0.01
Parlar 26	4.4 (<3.0–19)	4.2 (3.6–4.9)	6.0 (<3.0–13)	5.4 (4.7–6.3)	5.3 (<3.0–19)	5.0 (4.1–6.0)	0.06
Parlar 50	6.4 (<4.0–27)	6.0 (5.1–7.1)	8.5 (<4.0–23)	8.2 (7.2–9.4)	7.9 (<4–24)	7.4 (6.1–8.9)	0.048

[a] *P* values resulted from two-tailed Jonckheere–Terpstra trend test.

the associations between the subjects' characteristics and 18 compounds, a larger number than determined in similar, previously published studies. We have determined that the body burdens of these chemicals are associated with subjects' characteristics, such as age, pre-pregnancy body weight(s) and history/ies of past conception(s). Further studies are needed to evaluate the effects of these chemicals on the development of children, and further monitoring of human blood as well as foods and environments should be conducted.

Funding source

This study was supported by the following grants-in-aid for scientific research: 13307015, 16209022, 19209024 and 20590626.

Ethics

This study was conducted with all the subjects' written informed consent and was approved by the institutional ethical board for epidemiological studies at the Hokkaido University Graduate School of Medicine.

Acknowledgments

This study was conducted as a part of the 'The Hokkaido Study on Environment and Children's Health', which was supported by grants-in-aid for scientific research 13307015, 16209022, 19209024 and 20590626.

Table 8
Concentrations of organochlorine pesticides in relation to pre-pregnant body weight (pg/g wet mass).

Compounds	T1: ≤49 kg (n = 66)		T2: 50–55 kg (n = 64)		T3: ≥56 kg (n = 56)		P value[a]
	Med (range)	GM (95% CI)	Med (range)	GM (95% CI)	Med (range)	GM (95% CI)	
DDTs							
o,p'-DDT	3.2 (<2.0–11)	3.2 (2.8–3.6)	3.7 (<2.0–13)	3.2 (2.8–3.8)	4.1 (<2–11)	3.8 (3.3–4.5)	0.03
p,p'-DDT	22 (6.8–120)	23 (20–26)	22 (5.6–70)	23 (20–26)	27 (8.1–105)	28 (24–32)	0.04
p,p'-DDD	1.4 (<1.0–7.2)	1.2 (1.0–1.5)	1.2 (<1.0–9.0)	1.1 (0.91–1.4)	1.5 (<1.0–5.5)	1.4 (1.2–1.7)	0.35
o,p'-DDE	1.4 (<1.0–5.7)	1.1 (0.95–1.3)	1.3 (<1.0–6.2)	1.1 (0.97–1.3)	1.6 (<1.0–4.6)	1.5 (1.3–1.7)	0.03
p,p'-DDE	550 (120–4600)	560 (480–650)	610 (120–2400)	620 (520–730)	690 (160–2200)	670 (570–800)	0.09
p,p'-DDE + *p,p'*-DDT	580 (130–4700)	580 (500–670)	630 (120–2500)	640 (540–760)	710 (170–2200)	700 (600–830)	0.08
Chlordanes							
cis-Chlordane	2.1 (<0.8–17)	2.2 (1.9–2.5)	2.1 (0.88–6.4)	2.1 (1.9–2.4)	2.0 (0.83–18)	2.1 (1.8–2.4)	0.57
trans-Chlordane	0.66 (<0.6–2.9)	0.64 (0.54–0.76)	0.65 (<0.60–3.8)	0.63 (0.53–0.74)	<0.60 (<0.60–2.1)	0.51 (0.43–0.61)	0.07
Oxychlordane	42 (9.4–250)	41 (36–48)	43 (14–110)	42 (37–47)	38 (7.9–200)	38 (33–43)	0.44
cis-Nonachlor	10 (1.6–34)	10 (8.7–12)	11 (2.4–28)	10 (8.8–12)	11 (2.0–38)	11 (9.3–12)	0.47
trans-Nonachlor	68 (14–490)	73 (63–85)	73 (21–200)	73 (64–83)	68 (17–510)	69 (59–79)	0.64
cis-Heptachlorepoxide	26 (7.1–150)	27 (24–30)	28 (9.8–73)	27 (24–30)	32 (8.4–200)	32 (27–37)	0.09
Dieldrin	16 (7.5–52)	16 (14–18)	18 (5.8–59)	17 (15–19)	21 (9.7–54)	21 (19–23)	<0.01
HCB	96 (37–250)	99 (90–110)	100 (47–190)	100 (95–110)	110 (35–190)	100 (95–110)	0.25
HCHs							
β-HCH	140 (32–770)	130 (110–160)	150 (34–530)	150 (130–180)	170 (20–1200)	170 (140–210)	0.046
γ-HCH	1.4 (<1.0–7.2)	1.3 (1.1–1.5)	1.2 (<1.0–6.7)	1.2 (0.96–1.4)	1.1 (<1.0–100)	1.1 (0.88–1.4)	0.15
Mirex	6.8 (2.3–24)	6.8 (6.0–7.8)	5.9 (<2.0–30)	6.0 (5.2–7.0)	5.7 (1.9–21)	5.7 (5.0–6.5)	0.06
Parlar 26	4.3 (<3.0–19)	4.1 (3.5–4.9)	5.3 (<3.0–14)	4.4 (3.7–5.1)	5.7 (<3.0–19)	6.2 (5.3–7.2)	<0.01
Parlar 50	6.4 (<4.0–27)	6.1 (5.2–7.2)	8.3 (<4.0–21)	6.6 (5.6–7.9)	8.4 (<4.0–24)	8.7 (7.5–10)	<0.01

[a] *P* values resulted from two-tailed Jonckheere–Terpstra trend test.

Table 9
Concentrations of organochlorine pesticides in relation to pre-pregnant BMI (pg/g wet mass).

Compounds	T1: <19.9 (n = 62)		T2: 19.9–21.5 (n = 62)		T3: >21.5 (n = 62)		P value[a]
	Med (range)	GM (95% CI)	Med (range)	GM (95% CI)	Med (range)	GM (95% CI)	
DDTs							
o,p'-DDT	3.2 (<2.0–13)	3.3 (2.8–3.8)	3.7 (<2.0–9.1)	3.2 (2.8–3.8)	4.0 (<2.0–11)	3.6 (3.1–4.2)	0.16
p,p'-DDT	23 (6.8–120)	24 (20–27)	22 (5.6–63)	22 (20–25)	26 (8.1–100)	26 (23–30)	0.26
p,p'-DDD	1.4 (<1.0–7.2)	1.2 (1.0–1.5)	1.3 (<1.0–9.0)	1.2 (0.96–1.4)	1.4 (<1.0–6.1)	1.3 (1.1–1.6)	0.59
o,p'-DDE	1.3 (<1.0–6.2)	1.1 (0.9–1.3)	1.4 (<1.0–4.4)	1.2 (1.0–1.4)	1.5 (<1.0–4.6)	1.4 (1.2–1.6)	0.09
p,p'-DDE	550 (120–4600)	600 (500–710)	620 (120–2400)	590 (510–700)	680 (160–2400)	640 (540–760)	0.44
p,p'-DDE + *p,p'*-DDT	580 (130–4700)	620 (530–740)	640 (120–2500)	620 (530–720)	710 (170–2400)	670 (570–790)	0.41
Chlordanes							
cis-Chlordane	2.1 (0.8–17)	2.2 (1.9–2.6)	2.3 (<0.80–5.9)	2.1 (1.8–2.4)	2.0 (0.83–18)	2.1 (1.8–2.4)	0.48
trans-Chlordane	0.65(<0.60–2.5)	0.59 (0.50–0.70)	0.66 (<0.60–3.8)	0.65 (0.55–0.78)	0.41 (<0.60–2.1)	0.55 (0.46–0.65)	0.52
Oxychlordane	45 (12–250)	45 (39–52)	41 (9.4–94)	39 (34–45)	38 (7.9–200)	38 (33–43)	0.13
cis-Nonachlor	11 (3.2–34)	11 (9.4–13)	10 (1.6–28)	9.3 (8.1–11)	10 (2.0–38)	11 (9.3–12)	0.88
trans-Nonachlor	75 (27–490)	79 (68–91)	70 (14–170)	68 (60–77)	65 (17–510)	69 (60–79)	0.24
cis-Heptachlorepoxide	30 (7.1–150)	30 (26–34)	25 (9.8–71)	25 (22–28)	31 (8.4–200)	30 (26–35)	0.94
Dieldrin	17 (7.5–53)	17 (15–19)	16 (5.8–59)	16 (14–18)	21 (9.7–54)	21 (18–23)	0.02
HCB	110 (39–250)	100 (94–110)	100 (37–190)	98 (89–110)	110 (35–190)	100 (96–110)	0.84
HCHs							
β-HCH	140 (32–770)	140 (120–170)	140 (34–640)	150 (120–170)	160 (20–1200)	160 (140–200)	0.13
γ-HCH	1.3 (<1.0–7.2)	1.2 (1.0–1.5)	1.4 (<1.0–5.4)	1.2 (1.0–1.5)	1.1 (<1.0–100)	1.1 (0.87–1.4)	0.22
Mirex	7.0 (2.5–22)	7.0 (6.2–8.0)	5.9 (<2.0–30)	6.0 (5.2–7.0)	5.5 (<2.0–21)	5.6 (4.9–6.4)	<0.01
Parlar 26	5.2 (<3.0–19)	4.4 (3.7–5.2)	4.3 (<3.0–14)	4.1 (3.5–4.9)	5.7 (<3.0–19)	5.9 (5.1–6.9)	<0.02
Parlar 50	7.2 (<4.0–27)	6.4 (5.3–7.6)	7.2 (<4.0–22)	6.4 (5.4–7.6)	8.5 (<4.0–24)	8.5 (7.4–9.7)	0.04

[a] *P* values resulted from two-tailed Jonckheere–Terpstra trend test.

References

Ando M, Hirano S, Itoh Y. Transfer of hexachlorobenzene (HCB) from mother to newborn baby through placenta and milk. Arch Toxicol 1985;56:195–200.

Bachelet D, Truong T, Verner MA, Arveux P, Kerbrat P, Charlier C, et al. Determinants of serum concentrations of 1, 1-dichloro-2, 2-bis (*p*-chlorophenyl)ethylene and polychlorinated biphenyls among French women in the CECILE study. Environ Res. 2011;111:861–70.

Bennett DH, Scheringer M, McKone TE, Hungerbühler K. Predicting long-range transport: a systematic evaluation of two multimedia transport models. Environ Sci Technol 2001;35:1181–9.

Cao L-L, Yan CH, Yu X-D, Tian Y, Zhao L, Liu J-X, et al. Relationship between serum concentrations of polychlorinated biphenyls and organochlorine pesticides and dietary habits of pregnant women in Shanghai. Sci Total Environ 2011;409:2997–3002.

Carrizo D, Grimalt JO, Ribas-Fito N, Sunyer J, Torrent M. Physical-chemical and maternal determinants of the accumulation of organochlorine compounds in four-year-old children. Environ Sci Technol 2006;40:1420–6.

Cocco P, Fadda D, Ibba A, Melis M, Tocco MG, Atzeri S, et al. Reproductive outcomes in DDT applicators. Environ Res 2005;98:120–6.

Craan AG, Haines DA. Twenty-five years of surveillance for contaminants in human breast milk. Arch Environ Contam Toxicol 1998;35:702–10.

Dallaire F, Dewailly E, Laliberté C, Muckle G, Ayotte P. Temporal trends of organochlorine concentrations in umbilical cord blood of newborns from the lower north shore of the St. Lawrence river (Quebec, Canada). Environ Health Perspect 2002;110:835–8.

Elobeid MA, Padilla MA, Brock DW, Ruden DM, Allison DB. Endocrine disruptors and obesity an examination of selected persistent organic pollutants in the NHANES 1999–2002 data. Int J Environ Res Public Health 2010;7:2988–3005.

Eskenazi B, Marks AR, Bradman A, Fenster L, Johnson C, Barr DB, et al. In utero exposure to dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) and neurodevelopment among young Mexican American children. Pediatrics 2006;118:233–41.

Fernandez MF, Olmos B, Granada A, Lopez-Espinosa MJ, Molina-Molina JM, Fernandez JM. Human exposure to endocrine-disrupting chemicals and prenatal risk factors for cryptorchidism and hypospadias: a nested case–control study. Environ Health Perspect 2007;115(Suppl. 1):8–14.

Fukata H, Omori M, Osada H, Todaka E, Mori C. Necessity to measure PCBs and organochlorine pesticide concentrations in human umbilical cords for fetal exposure assessment. Environ Health Perspect 2005;113:297–303.
Haraguchi K, Koizumi A, Inoue K, Harada KH, Hitomi T, Minata M, et al. Levels and regional trends of persistent organochlorines and polybrominated diphenyl ethers in Asian breast milk demonstrate POPs signatures unique to individual countries. Environ Int 2009;35:1072–9.
Hardell E, Carlberg M, Nordström M, van Bavel B. Time trends of persistent organic pollutants in Sweden during 1993–2007 and relation to age, gender, body mass index, breast-feeding and parity. Sci Total Environ 2010;408:4412–9.
Hue O, Marcotte J, Berrigan F, Simoneau M, Doré J, Marceau P, et al. Plasma concentration of organochlorine compounds is associated with age and not obesity. Chemosphere 2007;67:1463–7.
Iwasaki M, Inoue M, Sasazuki S, Kurahashi N, Itoh H, Usuda M, et al. Plasma organochlorine levels and subsequent risk of breast cancer among Japanese women: a nested case–control study. Sci Total Environ 2008;402:176–83.
James RA, Hertz-Picciotto I, Willman E, Keller JA, Charles MJ. Determinations of serum polychlorinated biphenyls and organochlorine pesticides measured in women from the child health and development study cohort, 1973–1967. Environ Health Perspect 2002;110:617–24.
Keller JM, Kucklick JR, McClellan-Green PD. Organochlorine contaminants in loggerhead sea turtle blood: extraction techniques and distribution among plasma and red blood cells. Arch Environ Contam Toxicol 2004;46:254–64.
Kishi R, Sasaki S, Yoshioka E, Yuasa M, Sata F, Saijo Y, et al. Cohort profile: The Hokkaido Study on Environment and Children's Health in Japan. Int J Epidemiol 2011;40:611–8.
Konishi Y, Kuwabara K, Hori S. Continuous surveillance of organochlorine compounds in human breast milk from 1972 to 1998 in Osaka, Japan. Arch Environ Contam Toxicol 2001;40:571–8.
Konishi K, Sasaki S, Kato S, Ban S, Washino N, Kajiwara J, et al. Prenatal exposure to PCDDs/PCDFs and dioxin-like PCBs in relation to birth weight. Environ Res 2009;109:906–13.
Kress K, Zack MM, Kimbrough RD, Needham LL, Smrek AL, Jones BT. Cross-sectional study of a community with exceptional exposure to DDT. JAMA 1981;245:1926–30.
Lackmann GM. Neonatal serum *p,p′*-DDE concentrations in Germany: chronological changes during the past 20 years and proposed tolerance level. Paediatr Perinat Epidemiol 2005;19:31–5.
Longnecker MP, Klebanoff MA, Zhou H, Brock JW. Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. Lancet 2001;358:110–4.
Medehouenou TC, Ayotte P, Carmichael PH, Kröger E, Verreault R, Lindsay J, et al. Polychlorinated biphenyls and organochlorine pesticides in plasma of older Canadians. Environ Res 2011;111:1313–20.
Ministry of the Environment. Heisei 14, monitoring. Chemicals in the environment, Heisei 16; 2005.
Ministry of the Environment. Heisei 16, monitoring. Chemicals in the environment, Heisei 17; 2006.
Nakajima S, Saijo Y, Kato S, Sasaki S, Uno A, Kanagami N, 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;114:773–8.
Ostrea Jr EM, Bielawski DM, Posecion Jr NC, Corrion M, Villanueva-Uy E, Bernardo RC, et al. Combined analysis of prenatal (maternal hair and blood) and neonatal (infant hair, cord blood and meconium) matrices to detect fetal exposure to environmental pesticides. Environ Res 2009;109:116–22.
Pathak R, Mustafa M, Ahmed RS, Tripathi AK, Guleria K, Banerjee BD. Association between recurrent miscarriages and organochlorine pesticide levels. Clin Biochem 2010;43:131–5.
Pathak R, Mustafa MD, Ahmed T, Ahmed RS, Tripathi AK, Guleria K, et al. Intra uterine growth retardation: association with organochlorine pesticide residue levels and oxidative stress markers. Reprod Toxicol 2011;31:534–9.
Ribas-Fito N, Sala M, Cardo E, Mazon C, De Muga ME, Verdu A, et al. Association of hexachlorobenzene and other organochlorine compounds with anthropometric measures at birth. Pediatr Res 2002;52:163–7.
Ribas-Fito N, Torrent M, Carrizo D, Munoz-Ortiz L, Julvez J, Grimalt JO, et al. In utero exposure to background concentrations of DDT and cognitive functioning among preschoolers. Am J Epidemiol 2006;164:955–62.
Routti H, Arukwe A, Jenssen BM, Letcher RJ, Nyman M, Bäckman C, et al. Comparative endocrine disruptive effects of contaminants in ringed seals (Phocahispida) from Svalbard and the Baltic Sea. Comp Biochem Physiol C Toxicol Pharmacol 2010;152:306–32.
Sasaki K, Ishizaka T, Suzuki T, Takeda M, Uchiyama M. Accumulation levels of organochlorine pesticides in human adipose tissue and blood. Bull Environ Contam Toxicol 1991;46:662–9.
Saxena MC, Siddiqui MK, Bhargava AK, Murti CR, Kutty D. Placental transfer of pesticides in humans. Arch Toxicol 1981;48:127–34.
Schade G, Heinzow B. Organochlorine pesticides and polychlorinated biphenyls in human milk of mothers living in northern Germany: current extent of contamination, time trend from 1986 to 1997 and factors that influence the levels of contamination. Sci Total Environ 1998;215:31–9.
Schildkraut JM, Demark-Wahnefried W, DeVoto E, Hughes C, Laseter JL, Newman B. Environmental contaminants and body fat distribution. Cancer Epidemiol Biomarkers Prev 1999;8:179–83.
Siddiqui MK, Srivastava S, Srivastava SP, Mehrotra PK, Mathur N, Tandon I. Persistent chlorinated pesticides and intra-uterine foetal growth retardation: a possible association. Int Arch Occup Environ Health 2003;76:75–80.
Solomon GM, Weiss PM. Chemical contaminants in breast milk: time trends and regional variability. Environ Health Perspect 2002;110:A339–47.
Sugiura-Ogasawara M, Ozaki Y, Sonta S, Makino T, Suzumori K. PCBs, hexachlorobenzene and DDE are not associated with recurrent miscarriage. Am J Reprod Immunol 2003;50:485–9.
Tan J, Loganath A, Chong YS, Obbard JP. Exposure to persistent organic pollutants in utero and related maternal characteristics on birth outcomes: a multivariate data analysis approach. Chemosphere 2009;74:428–33.
Toft G, Thulstrup AM, Jönsson BA, Pedersen HS, Ludwicki JK, Zvezday V, et al. Fetal loss and maternal serum level of 2, 2′, 4, 4′, 5, 5′-hexachlorbiphenyl (CB-153) and 1, 1′-dichro-2, 2′-bis(p-chlorphenyl)ethylene (*p,p′*-DDE) exposure: a cohort study in Greenland and two European populations. Environ Health 2010;9:22–33.
Torres-Sánchez L, Zepeda M, Cebrian ME, Belkind-Gerson J, Garcia-Hernandez RM, Belkind-Valdovinos U, et al. Dichlorodiphenyldichloroethylene exposure during the first trimester of pregnancy alters the anal position in male infants. Ann NY Acad Sci 2008;1140:155–62.
Torres-Sánchez L, Schnaas L, Cebrián ME, Hernández Mdel C, Valencia EO, Garcia-Hernández RM. Prenatal dichlorodiphenydichloroethylene (DDE) exposure and neurodevelopment: a follow-up from 12 to 30 months of age. Neurotoxicology 2009;30:1162–5.
Washino N, Saijo Y, Sasaki S, Kato S, Ban S, Konishi K, et al. Correlations between prenatal exposure to perfluorinated chemicals and reduced fetal growth. Environ Health Perspect 2009;117:660–7.
Wittsiepe J, Schrey P, Lemm F, Eberwein G, Wilhelm M. Polychlorinated dibenzo-p-dioxins/polychlorinated dibenzofurans (PCDD/Fs), polychlorinated biphenyls (PCBs), and organochlorine pesticides in human blood of pregnant women from Germany. J Toxicol Environ Health A 2008;71:703–9.
Wong MH, Leung AO, Chan JK, Choi MP. A review on the usage of POP pesticides in China, with emphasis on DDT loadings in human milk. Chemosphere 2005;60:740–52.
Yamaguchi S, Kaku S, Kuwahara Y, Yamada A. Epidemiological findings and evaluation of the amount of organochlorine pesticides in human blood plasma in Japan. Arch Environ Contam Toxicol 1975;3:448–60.

総　説

北海道公衆衛生学雑誌
25：53 ～ 59，2011

注意欠如・多動性障害（ADHD）の有病率と養育環境要因に関する文献Review

池野　多美子[1)]，小林　澄貴[2)]，馬場　俊明[2)]，岸　玲子[1)]

要　旨

本総説では，ADHDの有病率に関する近年の動向，ADHDと養育環境に関する文献を概観して，今後の研究の課題を探ることを目的とした．その結果，ADHDの有病率は日本では３～７％前後の報告が多いが，正確な疫学データはなかった．有病率は，用いる診断基準の違い，診断的情報（評価指標など）の入手方法により差が生じると考えられ，統一された診断基準を用いた児童精神専門家による診断が望ましい．

環境要因は，喫煙を中心に養育環境との関連を検索した結果，妊婦の喫煙がADHDと関連していた．しかし，曝露評価が自記式である，曝露時期が妊娠中に限られている，受動喫煙の影響が検討されていない，サンプル数の少ない研究が多いなどの課題があった．今後は出生前後の生体試料を用いた喫煙曝露評価を行い，ADHDへの影響を再評価する必要がある．他の養育環境要因では母性的暖かさや授乳期間がADHD症状を緩和するとの報告があった．

Key words：注意欠如・多動性障害（ADHD），有病率，喫煙，養育環境

Ⅰ．緒　言

近年，発達障害殊に知能の遅れがない自閉症スペクトラムや注意欠如・多動性障害（Attention-Deficit/Hyperactivity Disorder; ADHD）など軽度の発達障害が年々増えている．相原らは特別支援教育を希望する児童生徒数が増えている現状を検証し[1)]，小児療育施設における14年間の発達障害初診患者の総数は，平成12年頃より増加傾向を認め，平成18年より急激な増加が認められたと報告している．診断別ではADHD，広汎性発達障害，学習障害が7割を超えてきていた．

ADHDは，７歳以前より認められる発達水準にそぐわない不注意，多動，衝動性を主症状とする障害で，診断は7歳以降に確定される疾患である．自閉症スペクトラムや学習障害（LD）などに比べて頻度の高い疾患であり，かつ遺伝的素因が強く影響すると言われる．注意力や多動性などは幼児期に一般的な行動であり，発育と共に消失し社会に馴染んでゆける児童がいる一方で，青年期や成人におけるADHDも少なくない．児の学校生活適応だけでなく，成人期にかけて就労や社会生活に関する適応も含めADHDは社会的問題といえる．

ADHDの疾病概念は，1902年にStill,G.Fが「道徳的統制の異常な欠陥」として報告して以降，微細脳機能障害（1962年，国際小児神経学会議）として，脳の障害に分類されてきた．診断基準に基づく疾病概念の変遷を表1に示した．1968年，DSM-Ⅱにおいて小児期の多動性反応と位置づけられてからは，WHOのICD-9においても多動を中心とした発達障害として扱われた．年数の経過と伴に，多動の症状をもつ子どもたちの症例が蓄積され，DSM-Ⅳの改訂で「不注意」「多動性」「衝動性」の主症状とその組み合わせによる下位分類を設定するに至った．しかし，近年青年期，成人期のADHDの増加により，診断基準と合致しない症例も見られ，DSM-Ⅴの改訂が注目されている．

本研究では，ADHDについて有病率を始めとする近年の動向，喫煙を中心としたADHD発症と養育環境に関する先行研究を調べ，今後の研究の課題を探ることを目的とする．

Ⅱ．有病率

ADHDの有病率については，『注意欠如・多動性障害-ADHD-の診断・治療ガイドライン』[2)]，吉益ら[3)]，渡部[4)]

1）北海道大学環境健康科学研究教育センター
2）北海道大学大学院医学研究科予防医学講座公衆衛生学分野
連絡先：池野多美子
〒060-0812　北海道札幌市北区北12条西７丁目
北海道大学中央キャンパス総合研究棟１号館
北海道大学環境健康科学研究教育センター
ＴＥＬ：011-706-4748
ＦＡＸ：011-706-4725
E-mail：tikeno@cehs@hokudai.ac.jp

受理日：平成24年１月10日

表1　疾病概念の変遷

年	診断基準*	診断名・改訂内容
1968	DSM-Ⅱ	小児期の多動性反応
1977	ICD-9	多動症候群
1980	DSM-Ⅲ	多動を伴う／多動を伴わない注意欠陥障害
	DSM-Ⅲ-R	注意欠陥障害：多動を伴うものに限定する
1989	ICD-10	多動症候群
1994	DSM-Ⅳ	注意欠陥／多動性障害:「不注意」「多動性」「衝動性」の主症状記載と症状の組み合わせによる「多動性－衝動性優勢型」「混合型」「不注意優勢型」の３下位分類設定
2000	DSM-Ⅳ-TR	注意欠陥／多動性障害：サブタイプの明確化、疫学的データや成人のADHDの附記
2013（予定）	DSM-Ⅴ	注意欠如・多動性障害**の診断分類の改定が予定されている

*　DSM：米国精神医学会 精神疾患の分類と診断の手引き；ICD：WHO国際疾病分類
**　ADHDの訳語は『精神神経学用語集　改訂６版』（2008）において「注意欠陥/多動性障害」から「注意欠如・多動性障害」へと修正された

らの総説を参考にし，成長に伴う有病率の変化，性差，地域差などを整理した．

（１）有病率

学童期の有病率は，ICD-10では多動性障害は1.5%，DSM-Ⅳでは3～5，DSM-Ⅳ-TRでは3～7%となっている[4]．Polanczyk[5]らは世界の７地域（北米，欧州，アジア，オセアニア，アフリカ，中東）における児童・思春期の子供を対象とした102編（対象者数171,756名）の研究を検討した結果，有病率は5.3%と見積もった．

ADHDが目立ってくるのは２～４歳頃と言われるが，米国での地域における就学前の疫学研究では罹病率は2～6%であり[6]，年長児の罹病率と変わらない．学童期にADHDの診断を受けた者の30～50%前後が成人期にも移行するとの報告があり[7]，最近の研究ではDopheideら[8]が，学童期の有病率は６～９%で，ADHD児の６～８割は思春期にも機能障害が残り，半数は成人まで症状が持続すると報告している．ADHD児を前向きに追跡した研究には，The Montreal Study，The New York Study，The Milwaukee Study，Swedish Studyなどがあり，診断基準と評価者（自分か親の評価か）の違いはあるが，いずれも20歳代でも最大66%にADHDの症状が持続している．

有病率の不一致について，Polanczykらは，①診断基準の違い（DSM-Ⅲ，DSM-Ⅳ，ICD-10か），②診断的情報の入手方法(回答は親のみか教師のみか，小児科医か)，③診断がなされるために（行動）機能障害を必要としているかによって影響を受けると指摘している．吉益もまた，有病率で留意すべきことは，児童精神科医による適切な判断が必須であると指摘している．その理由は，Polanczykらとも共通している部分があるが，子どもが発達段階で適切であるか否か判断することの難しさ，場面により行動が異なる場合，評価者の情報源（親のみか教師のみか）により子どもの状態を把握することの難しさ，広汎性発達障害との鑑別の重要性をあげている．評価者については，岡田ら[9]も，教師評定と保護者評定の差異について報告し，差異が生じる要因として，教室場面と家庭場面で児童・生徒が異なる行動特徴を示している可能性があることと，教師と保護者が異なる評価基準を持っている可能性があると考察している．

日本では正確な疫学データはないが，有病率は３～７%の範囲での報告が多い．小枝らは５歳児1,267名を対象にADHD（疑い含む）は4.7%（広汎性発達障害2.4%，学習障害0.2%）だったと報告した[10]．学童期の調査では，文部科学省の全国５地域の公立小中学校を対象とした調査（2002年）[11]を参考にすると，「知的発達に遅れはないものの学習面や行動面で著しい困難を示す」と担任が回答した割合は在籍児の6.3%にのぼり，16人に１人の割合で学級内に障害に応じた教育指導が必要とされる．ADHD児の長期的追跡はいまだ報告がないのが現状であるが増加が懸念されている．近年の有病率の増加傾向の原因として，湯汲英史[12]は①診断基準の変化（発達障害の概念が広がった），②障害観の変化（保護者の間で，発達障害への抵抗が薄れた），③教育制度の変化（特別支援教育の充実と，教育への期待の高まり），④育児能力の低下や子育てへの不安，⑤未熟児医療の進歩や低体重出生の増加などの複合的な要因を想定していた．学童期にADHDと診断された児の６～８割に障害が残り，さらに半数は成人期にも症状が継続しているということは，早期発見と早期介入がいかに重要であるかが窺われる．教育分野での発達障害支援の体制が整いつつありものの，体制拡充のためにも日本における疫学調査が必要と考えられる.同時に障害の特徴的行動が児の生育中の一過性のことなのか，個人差なのか，それとも障害につながるものか,経過を追って見極めることが大切である．

（２）性差

性差に関しては，ADHDは男児に多く女児の３～５

表2　妊娠期の喫煙とADHD（またはADHD関連症状）～前向きコーホート研究

著者／年／国	対象者	喫煙評価	アウトカム	ADHDの評価指標または診断基準	結果	調整因子
Fergusson ら／1993／New Zealand [12]	1,020人 8,10,12歳、男女	0，1－19，20本／日	行為障害、注意欠陥、破壊的行動	Rutterおよび Connerの質問紙	行為障害、注意欠陥、破壊的行動障害（行為障害＋注意欠陥）に有意に関連あり	性、人種、家族数、母親の年齢と学歴、経済状況、母親の養育態度、ライフイベント、10歳までに通った学校数、両親の不和や離婚、両親の薬物使用
Bor ら／1997／Australia [13]	5,296人 6か月→5歳	重度（7.3%） 中度（27.5%） なし（65.2%）	外面的および内面的問題行動、社会性または注意思考に関する問題	CBCL	3つのアウトカムいずれについても関連あり	なし
Weissman ら／1999／USA [14]	147人 6－23歳→17－36歳 男女	10本以上／日	ADHD	SADS-Life, Time Version, DSM-Ⅲ	男：13歳未満 RR=0.444 95%CI 0.094-2.09 女：13歳未満 RR=2.16 95%CI 0.135-34.71	子どもの精神状態に影響を与えうる両親の精神状態、人口統計的要因、周産期要因、家族要因のうち、妊娠期の母親と関係のあるもの、子どもの年齢と母親の大うつ病性障害
Breslau ら／2000／USA [15]	823人 6歳→11歳 男女	喫煙の有無	外面的および内面的問題行動、注意の問題	CBCL（母）、TRF(教師)	外面的問題行動に関連あり（p<0.05）	出生体重、評価者の違い、居住地、性、母親の学歴
Hill ら／2000／USA [16]	150人 8－18歳→18歳 男女	喫煙の有無	ADHD	K-SADS	有意な関連なし	妊娠中の飲酒、アルコール依存症の家族歴
Kotimaa ら／2003／Finland [17]	7,135人 0－8歳 男女	喫煙の有無	Hyperactivity	Rutter B2	OR=1.30 95%CI 1.1-4.1	性、家族構成、経済状況、母親の年齢、妊娠期の飲酒
Kahn ら／2003／USA [18]	161人 6か月→5歳 男女	喫煙の有無	ADHD	DSM-Ⅳ	多動及び衝動性と関連傾向あり（p<0.08）	生後の受動喫煙、経済状況、家庭環境、性、同胞数
Bastra ら／2003／Netherland [19]	1,186人 0→5.5→11歳 男女	0，1－5，6－10，11－19，20本以上／日	注意欠陥、外面・内面的問題行動、計算・所持障害	独自の作成による質問紙	内面的問題行動を除いて関連あり	社会経済状況、妊娠期の母親の精神障害および薬物使用などの周産期合併症
Obel ら／2007／Finland,Denmark [20]	20,936人** 7－15歳 男女	0，禁煙（妊娠前喫煙） 1－9本／10本以上）、 喫煙（妊娠中も喫煙） 1－9本／10本以上	ADHD	Rutters sacle（教師）またはSDQ（教師と母）、SDQ修正版（母）	非喫煙より禁煙・喫煙で有意にリスクが上昇 2つのコーホートで量反応性が認められた	性、妊娠中飲酒、両親の教育歴、家族構成、経済状況、出生体重
Cho ら／2010／Corea [21]	667人 8－11歳 男女	妊娠中の喫煙の有無 最近の喫煙曝露の有無 児の尿中コチニン	ADHD、神経認知学評価	K-ARS（両親、教師） Continuous Pergformance Test, Stroop Word and Color Test, Children's Color Trail Test	尿中コチニンは、ractivityとの関連が見られたが、調整後関連性は消失した尿中コチニンは調整後も神経認知学的能力との関連あり血中鉛は調整後もK-ARS,神経認知能力と関連）	性、年齢、父の教育歴、母のIQ、児のIQ、居住地、出生体重、血中鉛量****

*: CBCL: Child Behavior Check List; TRF: Teacher's Report Form ; K-SADS: Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version; DSM-Ⅳ: Diagnostic and Statistical Manual of Mental Disorder Version Ⅳ ; SDQ: Strengths and Difficulties Questionnaire

**：Northern Finnlish Birth Cohort, Aahus Birth Cohort, Healthy Habits for Two chohortを合計した数.分析はコーホートごとに行ったが,性別,家族構成,両親の教育歴,妊娠中の飲酒,出生体重,出生週数にコーホート間で差はなかった.

***2003年までの論文は吉武らの論文を一部改編し，以降の論文を追加した.

****鉛と喫煙曝露によるADHD発症リスクを検討．現在の曝露評価を血中鉛量,尿中コチニンで評価.

倍と言われ，Polanczykらは前出の102編の検討から男児は女児の2.45倍の有病率であると報告した．吉益らがメタアナリシスを行った結果，男子15.6%，女子8.5%，全体12.3%であった[3]．さらにADHDのタイプ別に男女比に関して分析を行い，女子に対する男子のオッズ比を算出した結果，不注意優勢型で2.05（95%CI 1.60-2.63），多動性 - 衝動性優勢型3.13（95%CI 1.90-5.20），混合型では3.61（95%CI 2.73-4.79），全体では2.25（95%CI 1.72-2.94）であった．この結果は従来の報告より低く，成人期に自己受診するADHDの男女比1.8-2.6[13]に近いと述べていた．

性差については，男児の方が多動や衝動性が女児より目立ちやすく，事例化しやすいことも影響していると考えられる[3]．

（3）地域差

地域差に関しては，アフリカが8.5%，南米が11.8%と高い有病率であった一方，アジアは4.0%，欧州は4.6%，北米は6.2%と低く，地域による差の大きさを報告している[8]．吉益らはDSM-Ⅳの診断基準を用いた論文をレビューし，地域・学校ベースの有病率を比較した[3]．ウクライナの地域在住10～12歳600名を対象に母親による質問票評価で19.8%と高かった一方，ブラジルの12～14歳1,013名を対象にした，教師と両親による質問評価では5.8%と低かった．ドイツ，インド，コロンビア，オーストラリアなどは有病率10%以上あり，Polanczykらの報告より全般的に高い．また同じ学校ベースの小学生以下を対象に教師による質問票評価で調査した研究において，有病率が6.8%（4,323名）と11.4%（8,253名）という報告もあり，地域による有病率の違いを示している．

Ⅲ．養育環境要因

ADHDの発症に関わる環境要因は，化学物質（農薬を含む）曝露，養育環境，社会環境要因などに分けて考える必要がある．ADHDは遺伝要因との関連が強い（76%）と言われ，環境-遺伝交互作用の検討も重要であるが，本研究では両親の生活習慣を含む養育環境を中心に検討した．

検索に際し，よりエビデンスレベルの高いコーホート研究・介入研究を検討することとした．英文の引用文献は，PubMedのデータベースを用いた．検索キーワードは，[Mesh]を使い，“Attention Deficit Hyperactivity Disorders”，“Smoking”または“Home environment”，“cohort study”，“Review or Systematic Review”とした．さらにヒト，英語，日本語，子ども（0-18歳）とした．日本語論文は，医中誌データベースを用い，同一の検索キーワードを用いた．期間は2011年までの10年間とした．

検索の結果，日常生活習慣を含んだ養育環境要因では，喫煙とADHDとの関連が47本あった．喫煙に関するReview論文は海外で23本，国内では1本であった．家庭環境では4本抽出された．児の生育時期により環境リスク全般について網羅的に検討した英文論文は4本であった．

（1）喫煙との関連

吉益は，1990～2004年に発表されたADHD関連行動と妊娠期の母親の喫煙との関連をコーホート研究や症例対照研究14本の研究について検討した．前向きコーホート研究に絞って，吉益らの報告以降の研究を追加し表2に示した[14-24]．多くの報告同様に妊娠中の喫煙がADHDと有意な関連を認めるものの，対象数の少ないものがあり，大半の研究が喫煙状況を聞き取り調査で評価し，ニコチンの代謝物であるコチニン測定を行っている研究はなかったと吉益は研究の課題を述べていた．Obelらは北欧の3つの前向きコーホート研究を比較検討し，まったく喫煙したことがない妊婦より，禁煙も含め妊娠中の喫煙がADHD発症リスクを上昇させることを明らかにした[22]．Choら[23]は8歳から11歳の667人を対象に，学童期の血中鉛と尿中コチニンを測定してADHDや神経認知能力と関連するか検討した．出生後の受動喫煙については，HermannがReviewした結果[24]，どちらも児の神経発達に影響していたことを報告していた．

出生前の喫煙との関連の研究が最も多く見られたが，Linnetや吉益が指摘するように，妊娠中の母親の喫煙状況を生体試料により客観的に評価した研究は乏しく，Choらが児の尿中コチニンを測定した1報告のみであった[23]．この研究は，受動喫煙の影響を生体試料で評価した点で貴重である．喫煙状況を聞き取りで調査すると思い出しバイアスに加え，妊婦の意識も反映される．Obelらの北欧のコーホート研究[22]では，妊娠中喫煙曝露評価を，妊娠16～34週に聞き取っており，思い出しバイアスの問題は除外できる．分析結果からは，妊娠を機に喫煙を中止しても，影響が残ることを明らかにした点は意義がある．とはいえ，胎児期曝露および児への曝露影響とADHDとの関連を解明するには，それぞれの時期の生体試料による曝露評価を行う必要がある．

（2）養育環境との関連

喫煙以外の養育環境の研究は4本抽出され，表3に示した．母親の温かさ（Tulluら[25]）や授乳期間の長さ（Julvetzら[26]）がADHD症状の緩和に関連していた．テレビやゲームの視聴時間は注意機能に関連しており，その影響は青年期も同様に認められた（Swing[27]）．また，Pelsserらはダイエットと ADHDとの関連について無作為化対照試験を実施し[28]，ADHD児への介入プログラム