We discovered that there are gender differences in the effects of dioxins and DL-PCBs on birth weight, infants' neurodevelopment and immune functions; our results suggest that the male infants are more susceptible to those chemicals than female infants. Our observations on birth weight were in concordance with other studies, which indicated a stronger negative effect of these compounds on the birth weight of male infants [66–70]. In our study, we found that the adjusted regression coefficients of total PCDDs TEQ and PCDDs/PCDFs TEQ levels among male and female infants were -331.4 and -126.3 g and -338.7 and -173.9 g, respectively. It is possible that male infants had lower birth weights at higher PCDDs and PCDDs/ PCDFs TEQ levels in the maternal blood than female infants. In addition to birth weight, we also found that dioxin-like compounds had negative effects on neurodevelopment at 6 months of age in addition to the negative effects on infants' immune function such as cord blood IgE levels and otitis media at 18 months of age. Although there are few epidemiological studies examining the effects of intrauterine exposure to dioxin-like compounds that specifically examined gender differences other than birth weight, it appears that male infants are more susceptible to exposure to these chemicals, which might be due to gender-specific endocrine activities. However, examining gender difference in the effects of PCBs and PCDDs/ PCDFs are part of a larger discussion on endocrine disruption; therefore, we need more evidence from larger studies with exposure measurements. Recently, we analyzed sex hormone concentrations in cord blood and its correlation with intrauterine EDCs exposure. In the near future, we will be able to examine gender-specific responses to EDCs and their effect on sex hormone levels. In addition to further epidemiological studies, molecular biological studies using animal models and human cell lines are also necessary to elucidate the molecular mechanisms of gender-dependent susceptibility to the exposures.

2. The different effects of dioxin congeners

We discovered that the different dioxin congeners had different effects on children exposed in utero. Identification of the potent biological properties of PCDDs, PCDFs and DL-PCBs, and which individual congeners of PCDDs, PCDFs and DL-PCBs affect birth outcomes has been an important goal in investigating the mechanism of effect to prevent harmful effects on fetuses. We found negative associations between maternal PCDF and PCDD exposure levels and birth weight and motor development at 6 months of age, and an increased risk of developing otitis media at 18 months of age correlated with maternal PCDF exposure.

In the study of Yu-Cheng children, it was indicated that the PCDFs group, including the penta-CDF and hexa-CDF congeners, were primarily responsible for the observed health effects compared to other groups of PCBs/PCDFs congeners [71]. Moreover, 70 % of the toxicity of TEQ was contributed by 2,3,4,7,8-PeCDF in Yusho patients [72]. These observations were in concordance with our results, which indicated a significant negative association between 2,3,4,7,8-PeCDF and birth weight. In addition, we found that maternal 2,3,4,7,8-PeCDF exposure increased the risk of developing otitis media at 18 months of age. These data suggest that 2,3,4,7,8-PeCDF is one of the most dangerous congeners.

Due to its high affinity for the AHR, it was suggested that there is a specific accumulation of

PCDDs and PCDFs congeners including 2,3,4,7,8-PeCDF in the placenta [73, 74], which plays an important role in transporting nutrients and oxygen through cord blood in the developing fetus. Taking the above considerations into account, we suggest that PCDDs and PCDFs congeners, especially 2,3,4,7,8-PeCDF, may accumulate in the placenta and retard important placental functions, which may result in lower birth weight.

We also found significant negative associations between motor development and maternal exposure to isomers of PCDDs and PCDFs and mental development and exposure to levels of total PCDDs and PCDFs. Currently, there were few human or animal experimental studies that have investigated the association between individual isomer levels of PCBs and dioxins and neurodevelopment. These studies are required to elucidate the mechanisms of action of individual congeners on neurodevelopment.

3. The diverse effects of PFCs exposure

Our results suggest that intrauterine PFCs exposure affects not only fetal growth but also the immune system. In the current study, cord blood IgE levels decreased significantly with high maternal PFOA concentrations in female infants. However, no association was observed between maternal serum PFOS and PFOA concentrations and the occurrence of food allergies, eczema, wheezing and otitis media in their infants during the first 18 months of life. The results of the C8 Health Project showed a significant trend in decreasing IgE levels with increasing PFOA levels in maternal blood samples among females [75]. Our results are consistent with those of that study, even though the concentration of maternal PFOA was lower than that measured in other studies, including the C8 Health Project [75–78]. However, we note that the PFOA levels were not associated with the development of allergies and infectious diseases in infants before 18 months of age. In addition, our result contradicted the results of the Taiwan study, which showed that PFOA levels were positively correlated with cord blood IgE levels only in males [21]. It may be necessary to perform follow-up studies to investigate whether prenatal exposure to PFCs affects immune system development (and address potential gender-specific differences) from infancy to school age because it is difficult to obtain definitive diagnoses for infants.

Moreover, a recent result from a prospective cohort study suggested that intrauterine exposure to PFCs could also modulate infants' thyroid hormone levels [19]. They reported that there were significant negative correlations between maternal PFOS and fetal T3, and maternal PFTrDA and fetal T4 and T3 after adjusting for major covariates. However, this was the only epidemiological report regarding prenatal PFCs exposure and infants' thyroid function, and their sample size was insufficient. Thus, we need additional epidemiological studies to validate the effects of intrauterine PFCs exposure on thyroid functions.

In addition, the temporal trends of PFCs levels indicates that PFOS and PFOA concentrations were decreasing every year from 2003 to 2011 due to the restriction of PFOS by the Stockholm Convention on Persistent Organic Pollutants in 2009. Instead, PFNA and PFDA, which have a longer carbon chain than PFOA and are harder to be metabolized in the body, were increasing. Further studies must be conducted to estimate the effects of intrauterine exposure to long-chained PFCs on children's

health and development.

4. Genetic susceptibility to the exposures

In our study, we found that the maternal genetic polymorphisms in AHR or CYP1A1 independently modified dioxin concentrations in maternal blood, suggesting different dioxin accumulation in the body of individuals with these genotypes, which would lead to different dioxin exposure levels [55]. CYP1A1 activation mediated by AHR is an important mechanism for metabolizing dioxins. Dioxins such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) are sensitive to AHR, and TCDD mediates transcriptional regulation of AHR via its binding with AHR nuclear translocator. Activated AHR facilitates the expression of CYP1A1, CYP1A2, CYP1B1 and AHRR, which are important for metabolizing dioxins [79]. Moreover, the expression of CYP1A1 and CYP1B1 are important for endocrine signaling pathways. Those proteins mediate the transformation of 17b-estradiol (E2)/estrone (E1) to the biologically active metabolites 2-hydroxyestradiol (2-OH–E2) and 4-hydroxyestradiol (4-OH–E2) [80].

In addition to the dioxin concentrations, among the polymorphism groups of CYP1A1, AHR, GSTM1 and NQO1, we observed different susceptibilities with respect to the effect of maternal smoking exposure on birth size [56, 57]. The AHR, CYP1A1 and GSTM1 metabolize the polycyclic aromatic hydrocarbon (PAH) in tobacco smoke. The GSTM1 detoxifies specific biologically active metabolites of PAHs, and carriers of the GSTM1 null genotype have a reduced ability to detoxify these metabolites. Our study shows that infants born to mothers that have the AHR wild genotype and continuously smoke had a significantly lower birth weight and length compared with infants born to non-smokers; moreover, smokers who had the AHR wild type and CYP1A1 variant genotype had the greatest reduction in both birth weight and length. Because there have only been a few epidemiological studies, further studies are required to clarify the role of the Arg554Lys polymorphism in fetal development.

The NQO1 is an important enzyme that functions in both phase I (activation) and phase II (detoxification) metabolism of xenobiotics depending on the substrate. As a detoxification enzyme, it catalyzes the two-electron reduction of quinoid compounds to the readily excreted hydroquinones to prevent the generation of reactive oxygen species and, thereby, protect cells against oxidative damage. It also catalyzes the activation of some pro-carcinogens such as nitrosamines and heterocyclic amines, which are present in tobacco smoke [81]. Our study suggests an important role for polymorphisms in the N-nitrosaminemetabolizing enzyme gene NQO1 in mitigating the adverse effects of maternal smoking on infant birth size. These findings could have significant public health implications regarding the need for smoking prevention and cessation programs aimed specifically at susceptible women of childbearing age.

In addition, our current results suggest that the adverse health effects of prenatal tobacco smoke exposure resulted not only from active smoking but also from secondhand smoke (SHS) exposure during pregnancy. Birth weight and infant length among SHS-exposed women with the CYP1A1*2C AG/GG genotypes (-88 g and -0.9 cm, respectively) and the epoxide hydrolase 1 (EPHX1) His/His genotypes (-154 g and -1.1 cm, respectively) were significantly lower. The N-acetyl transferase 2 (NAT2*7) slow acetylators group was also adversely affected (-51 g). A

combination of EPHX1 His/His?NAT2*7 slow alleles not only resulted in a remarkable decrease in birth weight and length (-145 g and -1.1 cm, respectively) but also demonstrated significant interaction with SHS exposure [82].

The future challenges of the study

1. Inferences from previous studies in hypospadias– gene–environment interactions

As described in our previous review, both genetic and environmental factors contribute to the etiology of congenital malformations such as hypospadias and cryptorchidism [26]. The etiology of hypospadias was unclear in a majority of cases, but it was regarded as a complex disorder caused by both genetic and environmental factors (Fig. 6). Because the development of the urethral and external genital system in the male fetus is androgendependent, abnormalities in the synthesis and metabolism of androgens caused by exposure to EDCs can result in abnormal genital developmental phenotypes.

In previous studies, we had clarified the etiology of hypospadias with genetic factors that were related to fetal endocrine activity such as the ESR1 and ESR2 and 17bHSD3 and maternal hormonal activity such as the CYP1A1 in a retrospective case–control study [23, 24, 26]. Hypospadias is a common congenital anomaly caused by an incomplete fusion of the urethral folds. The urethral opening is on the ventral surface of the penis, on the scrotum or the perineum. Thus far, an increase in the prevalence of hypospadias has been reported in various countries, and these trends are speculated to be related to EDC exposure [83]. Several studies have shown the association between hypospadias and fetal gene polymorphisms in genes involved in androgen metabolism [84–86].

These results suggest that environmental factors, including EDCs exposure in utero, as well as genetic factors are responsible for the etiologies of congenital malformations, diseases and birth outcomes such as birth size. Moreover, considering that environmental exposures in utero might affect the children's birth outcomes, the mother's EDCs exposure level and genetic factors that may affect the intrauterine environment are also important factors to consider in evaluating the cause of adverse birth outcomes. Thus, to elucidate the etiology of the disease, two different study approaches must be conducted; one is the screening for genetic risk factors in children and mothers, and the other is to estimate the effect of the environmental risk factors including EDC exposures. In addition, by integrating those two approaches to study gene–environment interaction, it becomes possible to identify more susceptible individuals in the population.

2. Gene–environment interactions involved in the etiology of ADHD

In recent years, the increased prevalence of developmental disorders such as Autism Spectrum Disorder (ASD) and ADHD are of increasing concern to the public. Although it is estimated that genetic effects account for 80 % of ASD cases and 79 % of ADHD cases, respectively [87], environmental factors such as the nursing environment and exposure to tobacco smoke also appear to be important factors because the prevalence of these diseases continues to increase while the genetic background of the population remains relatively stable. To date, postnatal environmental exposures, such as passive smoke exposure, iron deficiency, thyroid

dysfunction, otitis media and psychosocial stress, are reported as risk factors for ADHD. In addition, prenatal risk factors such as maternal smoking, maternal alcohol intake, lead, PCBs and food additive exposure are also reported to be risk factors for ADHD [88]. Additionally, several studies have indicated that children who were born prematurely or with low birth weight had an increased risk of developing ADHD [89–92], which suggests that the intrauterine environment may play some role. However, the detailed mechanisms of the etiology of those neurodevelopmental disorders have yet to be identified. In the future, by taking genetic and environmental study approaches and studying gene-environment interactions, it is anticipated that all possible risk factors will be elucidated, and eventually, the etiologies of developmental disorders such as Autism and ADHD will be known.

In the present cohort studies, we discovered the maternal genetic factors that affect a child's birth outcome along with the risks associated with maternal smoking and intrauterine dioxin exposure. However, there are few genetic risk factors that have been found thus far considering the large, intricate gene networks involved in a child's health and development. Further studies including genome wide analysis are needed to elucidate the effects of gene–environment interactions.

3. The role of epigenetics

Recently, there has been a growing interest in understanding the role of epigenetics in linking a child's intrauterine environment to future health and disease. Epigenetic modifications, such as DNA methylation, are programmed in utero and are likely to be maintained through cell division and throughout cell linages [93]. Therefore, it is postulated that epigenetic regulation is the "missing link" in the DOHaD hypothesis, which would connect the intrauterine environment to postnatal phenotypes. To date, dozens of animal studies and several epidemiological studies have been conducted to estimate the effect of maternal smoking, environmental chemical exposure and metal exposure in utero on a child's epigenome [94–96]. For instance, maternal smoking exposure increases the methylation of the regulatory region of Insulin-like Growth Factor 2 (IGF2) in cord blood DNA, which negatively correlates with IGF2 protein levels in the cord blood [97, 98]. However, at this moment, the epigenetic effects of intrauterine exposure to environmental chemicals are controversial. Further studies exploring the environmental and genetic risk factors for epigenetic vulnerability is necessary. Currently, we are conducting epigenetic research to investigate the effect of intrauterine exposures to environmental chemicals on a child's epigenome and the resulting risk for future health and disease complications.

As Barker first suggested, the consequences of a disrupted intrauterine environment might be expressed as adverse health outcomes a decade more or later. To thoroughly estimate the effects of intrauterine EDCs exposures in humans, it is necessary to follow individuals in a prospective birth cohort study with a sufficient sample size for a long period.

Working toward international collaboration

In recent years, there has been an avid movement toward collaborating and integrating existing birth cohort studies across borders. The primary purpose of these birth cohort consortiums are to obtain evidence based results

by using data from larger sample sizes (meta-analysis), as well as obtaining more applicable and generalizable results by integrating data beyond regions, countries and ethnicities. For instance, in Europe, the Environmental Health Risks in European Birth Cohorts (ENRIECO) was established in 2009 [99]. In Asia, the Birth Cohort Consortium of Asia (BiCCA) is now calling for participation to all existing Asian birth cohorts [http://www.bicca.org]. Although there are many challenges regarding coordination of different cohort studies, we do believe that it is a worthy endeavor.

Additional information concerning the Hokkaido study is available at the study website: http://www.cehs.hokudai. ac.jp/. All of the source data that have been collected are maintained and stored at Hokkaido University Center for Environmental and Health Sciences. Initial approaches or enquiries regarding the study can be made to the principal investigator (rkishi@med.hokudai.ac.jp).

Acknowledgments We would like to express our appreciation to all of the study participants of The Hokkaido Study on Environment and Children's Health. We express our profound gratitude to all personnel in the hospitals and clinics that collaborated with the study: Sapporo Toho Hospital, Keiai Hospital, Endo Kikyo Maternity Clinic, Shiroishi Hospital, Memuro Municipal Hospital, Aoba Ladies Clinic, Obihiro-Kyokai Hospital, Akiyama Memorial Hospital, Sapporo Medical University Hospital, Hokkaido University Hospital, Kitami Red Cross Hospital, Hoyukai Sapporo Hospital, Gorinbashi Hospital, Hashimoto Clinic, Asahikawa Medical College Hospital, Hakodate Central General Hospital, Ohji General Hospital, Nakashibetsu Municipal Hospital, Sapporo Tokushukai Hospital, Asahikawa Red Cross Hospital, Wakkanai City Hospital, Kushiro Rosai Hospital, Sapporo-Kosei General Hospital, Shibetsu City General Hospital, Nikko Memorial Hospital, Sapporo City General Hospital, Kohnan Hospital, Hakodate City Hospital, Hokkaido Monbetsu Hospital, Tenshi Hospital, Hakodate Goryoukaku Hospital, Nakamura Hospital, Kin-ikyo Sapporo Hospital, Kitami Lady's Clinic, Engaru-Kosei General Hospital, Kushiro Red Cross Hospital, Nayoro City General Hospital and Obihiro-Kosei General Hospital. We also deeply express our gratitude to all of the staff of The Hokkaido Study on Environment and Children's Health for their considerable efforts to support our study: Y. Tanabe, M. Kato, Y. Okada, K. Tanaka, M. Hoshiba, N. Takeshima and M. Kihara. This study was funded by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Health, Labor and Welfare; the Ministry of Education, Culture, Sports, Science and Technology; the Japan Society for the Promotion of Science; and the Ministry of Environment.

Conflict of interest None declared.

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

S. Tajima, H. Goudarzi, K. Azumi, A. Kanazawa, Y. Otake, T. A. Yila (Hokkaido University Center for Environmental and Health Sciences, Sapporo, Japan), Y. Ait Bamai, S. Cong, Tos. Baba, T. S. Braimoh, S. Ban, N. Washino, K. Konishi, S. Kato, A. Uno, M. Limpar (Department of Public Health Sciences, Hokkaido University Graduate School of Medicine, Sapporo), H. Minakami (Department

of Obstetrics and Gynecology, Hokkaido University Graduate School of Medicine, Sapporo), K. Nonomura (Department of Renal and Genitourinary Surgery, Hokkaido University Graduate School of Medicine, Sapporo), T. Mitsui (Department of Urology, Hokkaido University Graduate School of Medicine, Sapporo), T. Endo, Tsu. Baba (Sapporo Medical University, Sapporo), K. Sengoku, Y. Saijo, E. Yoshioka, T. Miyamoto (Asahikawa Medical University, Asahikawa), M. Yuasa (Juntendo University, Tokyo), F. Sata (Department of Epidemiology, National Institute of Public Health, Wako), N. Kurahashi (Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo), J. Tamaki (School of Medicine, Kinki University), J. Kajiwara, T. Todaka (Fukuoka Prefectural Institute of Health and Environmental Sciences, Fukuoka), H. Murohashi (Graduate School of Education, Hokkaido University, Sapporo), H. Matsuura (Laboratory of Bioorganic Chemistry, Division of Applied Bioscience, Research Faculty of Agriculture, Hokkaido University, Sapporo), T. Matsumura (IDEA Consultants,Inc., Shizuoka), M. Ishizuka (Laboratory of Toxicology, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo).

Collaborating Institutions

Hokkaido University Center for Environmental and Health Sciences; Hokkaido University Graduate School of Medicine: Departments of Public Health Sciences, Obstetrics and Gynecology, Pediatrics, Renal and Genitourinary Surgery, Respiratory Medicine and Dermatology; Hokkaido University Graduate School of Veterinary Medicine: Department of Environmental Veterinary Sciences; Hokkaido University Graduate School of Agricultures; Sapporo Medical University: Obstetrics and Gynecology; Asahikawa Medical College: Department of Health Sciences, Obstetrics and Gynecology; Sapporo City Institute of Public Health; Hokkaido Association of Obstetricians and Gynecologists; Fukuoka Institute of Health and Environmental Sciences; Hoshi University School of Pharmacy and Pharmaceutical Sciences, Department of Analytical Chemistry; IDEA Consultants, Inc., Sizuoka; Chubu University, Nagoya.

References

1. Colborn T, Dumanoski D, Myers JP. Our stolen future: are we threatening our fertility, intelligence, and survival? A scientific detective story. New York: Plume; 1997.
2. Wigle DT, Arbuckle TE, Turner MC, Berube A, Yang Q, Liu S, et al. Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. J Toxicol Environ Health B Crit Rev. 2008; 11(5–6):373–517.
3. Schug TT, Janesick A, Blumberg B, Heindel JJ. Endocrine disrupting chemicals and disease susceptibility. J Steroid Biochem Mol Biol. 2011;127(3–5):204–15.
4. Meeker JD. Exposure to environmental endocrine disruptors and child development. Arch Pediatr Adolesc Med. 2012;166(6):E1–7.
5. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet. 1986;1(8489):1077–81.
6. Gluckman P, Hanson M. Developmental origins of health and disease. New York: Cambridge University Press; 2006.
7. Newman J, Ross M. Early life origins of human health and disease. Basel: Karger; 2009.

8. Dietert RR. Developmental immunotoxicology: focus on health risks. Chem Res Toxicol. 2009;22(1):17–23.
9. El Majidi N, Bouchard M, Gosselin NH, Carrier G. Relationship between prenatal exposure to polychlorinated biphenyls and birth weight: a systematic analysis of published epidemiological studies through a standardization of biomonitoring data. Regul Toxicol Pharmacol. 2012;64(1):161–76.
10. Boucher O, Muckle G, Bastien CH. Prenatal exposure to polychlorinated biphenyls: a neuropsychologic analysis. Environ Health Perspect. 2009;117(1):7–16.
11. Goodman JE, Kerper LE, Boyce CP, Prueitt RL, Rhomberg LR. Weight-of-evidence analysis of human exposures to dioxins and dioxin-like compounds and associations with thyroid hormone levels during early development. Regul Toxicol Pharmacol. 2010;58(1):79–99.
12. Vreugdenhil HJ, Slijper FM, Mulder PG, Weisglas-Kuperus N. Effects of perinatal exposure to PCBs and dioxins on play behavior in Dutch children at school age. Environ Health Perspect. 2002;110(10):A593–8.
13. Su PH, Huang PC, Lin CY, Ying TH, Chen JY, Wang SL. The effect of in utero exposure to dioxins and polychlorinated biphenyls on reproductive development in eight year-old children. Environ Int. 2012;39(1):181–7.
14. Winans B, Humble MC, Lawrence BP. Environmental toxicants and the developing immune system: a missing link in the global battle against infectious disease? Reprod Toxicol. 2011;31(3): 327–36.
15. Apelberg BJ, Witter FR, Herbstman JB, Calafat AM, Halden RU, Needham LL, 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(11): 1670–6.
16. Fei C, McLaughlin JK, Tarone RE, Olsen J. Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort. Environ Health Perspect. 2007;115(11):1677–82.
17. Olsen GW, Butenhoff JL, Zobel LR. Perfluoroalkyl chemicals and human fetal development: an epidemiologic review with clinical and toxicological perspectives. Reprod Toxicol. 2009; 27(3–4):212–30.
18. Halldorsson TI, Rytter D, Haug LS, Bech BH, Danielsen I, Becher G, et al. Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort study. Environ Health Perspect. 2012;120(5):668–73.
19. Kim S, Choi K, Ji K, Seo J, Kho Y, Park J, et al. Trans-placental transfer of thirteen perfluorinated compounds and relations with fetal thyroid hormones. Environ Sci Technol. 2011;45(17): 7465–72.
20. Grandjean P, Andersen EW, Budtz-Jorgensen E, Nielsen F, Molbak K, Weihe P, et al. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA. 2012;307(4):391–7.
21. Wang IJ, Hsieh WS, Chen CY, Fletcher T, Lien GW, Chiang HL, et al. The effect of prenatal perfluorinated chemicals exposures on pediatric atopy. Environ Res. 2011;111(6):785–91.
22. World Health Organization. Possible developmental early effects of endocrine disrupters on child health. Geneva: WHO Press; 2012.
23. Ban S, Sata F, Kurahashi N, Kasai S, Moriya

K, Kakizaki H, et al. Genetic polymorphisms of ESR1 and ESR2 that may influence estrogen activity and the risk of hypospadias. Hum Reprod. 2008;23(6):1466–71.

24. Sata F, Kurahashi N, Ban S, Moriya K, Tanaka KD, Ishizuka M, et al. Genetic polymorphisms of 17 beta-hydroxysteroid dehydrogenase 3 and the risk of hypospadias. J Sex Med. 2010;7(8): 2729–38.
25. Kurahashi N, Sata F, Kasai S, Shibata T, Moriya K, Yamada H, et al. Maternal genetic polymorphisms in CYP1A1, GSTM1 and GSTT1 and the risk of hypospadias. Mol Hum Reprod. 2005; 11(2):93–8.
26. Kishi R, Sata F, Yoshioka E, Ban S, Sasaki S, Konishi K, et al. Exploiting gene-environment interaction to detect adverse health effects of environmental chemicals on the next generation. Basic Clin Pharmacol Toxicol. 2008;102(2):191–203.
27. 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(3):611–8.
28. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet 1998;351(9111):1225–32.
29. Konishi H. A manual for the diagnoses of congenital anomalies (Gaihyou kikei sindan-no tebiki). Kanagawa, Japan: the study group on congenital anomalies in Kanagawa; 1981 (in Japanese).
30. Nishima S, Chisaka H, Fujiwara T, Furusho K, Hayashi S, Hiraba K, et al. Surveys on the prevalence of pediatric bronchial asthma in Japan: a comparison between the 1982, 1992, and 2002 surveys conducted in the same region using the same methodology. Allergol Int. 2009;58(1):37–53.
31. Okada E, Sasaki S, Saijo Y, Washino N, Miyashita C, Kobayashi S, et al. Prenatal exposure to perfluorinated chemicals and relationship with allergies and infectious diseases in infants. Environ Res. 2012;112:118–25.
32. Yamada T, Morikawa M, Yamada T, Kishi R, Sengoku K, Endo T, et al. First-trimester serum folate levels and subsequent risk of abortion and preterm birth among Japanese women with singleton pregnancies. Arch Gynecol Obstet. 2013;287(1):9–14.
33. Iida T, Todaka T. Measurement of dioxins in human blood: improvement of analytical method. Ind Health. 2003;41(3): 197–204.
34. Todaka T, Hirakawa H, Kajiwara J, Hori T, Tobiishi K, Onozuka D, 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(8):1228–37.
35. Todaka T, Hirakawa H, Kajiwara J, Onozuka D, Sasaki S, Miyashita C, et al. Concentrations of polychlorinated dibenzo-pdioxins, polychlorinated dibenzofurans, and polychlorinated biphenyls in blood and breast milk collected from pregnant women in Sapporo City, Japan. Chemosphere. 2011;85(11): 1694–700.
36. Todaka T, Hirakawa H, Tobiihi K, Iida T. New protocol of dioxins analysis in human blood. Fukuoka Igaku Zasshi. 2003;94(5):148–57.
37. Todaka T, Hori T, Hirakawa H, Kajiwara J, Yasutake D, Onozuka D, 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(6):923–31.

38. Van den Berg M, Birnbaum LS, Denison M, De Vito M, Farland W, Feeley M, et al. The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol Sci. 2006;93(2): 223–41.
39. Inoue K, Okada F, Ito R, Kato S, Sasaki S, Nakajima S, 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(11):1204–7.
40. Inoue K, Okada F, Ito R, Kawaguchi M, Okanouchi N, Nakazawa H. Determination of perfluorooctane sulfonate, perfluorooctanoate and perfluorooctane sulfonamide in human plasma by column-switching liquid chromatography-electrospray mass spectrometry coupled with solid-phase extraction. J Chromatogr B Anal Technol Biomed Life Sci. 2004;810(1):49–56.
41. Kashino I, Okada E, Matsuura H. Development of UPLC-MS/MS for the determination of eleven PFC in human plasma. In: Proceedings of Japan Society for Environmental Chemistry, Ehime, Japan, 11–13 July, 2012.
42. Kanazawa A, Miyasita C, Okada E, Kobayashi S, Washino N, Sasaki S, et al. Blood persistent organochlorine pesticides in pregnant women in relation to physical and environmental variables in The Hokkaido Study on Environment and Children's Health. Sci Total Environ. 2012;426:73–82.
43. Konishi K, Sasaki S, Kato S. Effect of prenatal exposure to dioxins on birth weight. In: Proceedings of Persistent Organic Pollutants (POPs) Research in Asia, 2008, pp 362–67.
44. Konishi K, Sasaki S, Kato S, Ban S, Washino N, Kajiwara J, et al. Effects of prenatal exposure to dioxins and methyl mercury on birth weight. Organohalogen Compd. 2007;69:2109–11.
45. Ito Y, Yokota H, Wang R, Yamanoshita O, Ichihara G, Wang H, et al. Species differences in the metabolism of di(2-ethylhexyl) phthalate (DEHP) in several organs of mice, rats, and marmosets. Arch Toxicol. 2005;79(3):147–54.
46. Tsuboi T, Kawai T, Araki A, Kishi R. Determination of human urinary metabolites of five phthalate by GC/MS—study of elementally school children in Sapporo, Japan. In: Proceedings of International Society of Exposure Science, Seattle, USA, 2012, p. 40.
47. Araki A, Kawai T, Tsuboi T, Ait Bamai Y, Takeda T, Yoshioka E, et al. Determination of phthalate metabolites in urine of children and their family—exposure assessment to plasticizer and flame retardants and their risk on children. In: Proceedings of International Society of Exposure Science, Seattle, USA, 2012, p. 72.
48. Yamamoto J, Hayama S, Sato N, Matsumura T, Kishi R, Sasaki S, et al. Analysis of bisphenol A in biological sample. In: Proceedings of 20th Symposium on Environmental Chemistry, Kumamoto, Japan, 2011, pp 610–11.
49. Sasaki S, Braimoh TS, Yila TA, Yoshioka E, Kishi R. Selfreported tobacco smoke exposure and plasma cotinine levels during

pregnancy—a validation study in Northern Japan. Sci Total Environ. 2011;412–413:114–8.

50. Kashima H, Kato M, Handa T. Neuropsychological investigation of the frontal function in chronic schizophrenia: results of a modified Wisconsin card sorting test. Jpn J Clin Psychiatry. 1985;14:1479–89 (in Japanese).

51. Kashima H, Kato M. Wisconsin card sorting test (Keio Version) (KWCST). Brain Sci Ment Disord. 1995;6:209–16 (in Japanese). 52. Sasaki S. Nihongoban yoshokisei yakuwari kodo shakudo (J-PSAI) no sakusei: pre-School Activities Inventory no hoyaku. Stud Sociol Psychol Educ Inq Hum Soc. 2006;62:174–6.

53. Anme T, Shimada C, Katayama H. Evaluation of environmental stimulation for 18 months and the related factors. Nihon Koshu Eisei Zasshi. 1997;44(5):346–52.

54. Shiokawa H. Development of the life event questionnaire for parents: its use and reliability data. Jichi Med Univ J. 2007;30:165–72.

55. Kobayashi S, Sata F, Sasaki S, Ban S, Miyashita C, Okada E, et al. Genetic association of aromatic hydrocarbon receptor (AHR) and cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1) polymorphisms with dioxin blood concentrations among pregnant Japanese women. Toxicol Lett. 2013;219(3): 269–78.

56. Sasaki S, Kondo T, Sata F, Saijo Y, Katoh S, Nakajima S, 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(2):77–83.

57. Sasaki S, Sata F, Katoh S, Saijo Y, Nakajima S, Washino N, 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(6): 719–26.

58. Yila TA, Sasaki S, Miyashita C, Braimoh TS, Kashino I, Kobayashi S, et al. Effects of maternal 5,10-methylenetetrahydrofolate reductase C677T and A1298C Polymorphisms and tobacco smoking on infant birth weight in a Japanese population. J Epidemiol. 2012;22(2):91–102.

59. 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(7):906–13.

60. 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(5): 773–8.

61. Washino N, Saijo Y, Konishi K. The effect of prenatal exposure to dioxins on cord serum IGE. In: Proceedings of the 27th International Symposium on Halogenated Persistent Organic Pollutants, Tokyo, Japan, 2–7 September, 2007

62. Miyashita C, Sasaki S, Saijo Y, Washino N, Okada E, Kobayashi S, et al. Effects of prenatal exposure to dioxin-like compounds on allergies and infections during infancy. Environ Res. 2011;111(4):551–8.

63. 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(4):660–7.

64. Okada E, Kashino I, Matsuura H, Sasaki S, Miyashita C, Yamamoto J, et al. Temporal trends of perfluoroalkyl acids in plasma samples of pregnant women in Hokkaido, Japan, 2003–2011. Environ Int. 2013 (in press).
65. Okada E, Kashino I, Sasaki S, Miyashita C, Ikeno T, Araki A, et al. Relationship between prenatal exposure to perfluorinated compounds and allergic diseases in infants. In: Proceedings of International Society for Environmental Epidemiology, Basel, Switzerland, August, 2013
66. Rylander L, Stromberg U, Hagmar L. Dietary intake of fish contaminated with persistent organochlorine compounds in relation to low birthweight. Scand J Work Environ Health. 1996;22(4):260–6.
67. Baibergenova A, Kudyakov R, Zdeb M, Carpenter DO. Low birth weight and residential proximity to PCB-contaminated waste sites. Environ Health Perspect. 2003;111(10):1352–7.
68. Sonneborn D, Park HY, Petrik J, Kocan A, Palkovicova L, Trnovec T, et al. Prenatal polychlorinated biphenyl exposures in eastern Slovakia modify effects of social factors on birthweight. Paediatr Perinat Epidemiol. 2008;22(3):202–13.
69. 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(5): 648–56.
70. Vartiainen T, Jaakkola JJ, Saarikoski S, Tuomisto J. 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(2):61–6.
71. Guo YL, Lambert GH, Hsu CC, Hsu MM. Yucheng: health effects of prenatal exposure to polychlorinated biphenyls and dibenzofurans. Int Arch Occup Environ Health. 2004;77(3):153–8.
72. Masuda Y. Fate of PCDF/PCB congeners and change of clinical symptoms in patients with Yusho PCB poisoning for 30 years. Chemosphere. 2001;43(4–7):925–30.
73. Wang SL, Lin CY, Guo YLL, Lin LY, Chou WL, Chang LW. Infant exposure to polychlorinated dibenzo-p-dioxins, dibenzofurans and biphenyls (PCDD/Fs, PCBs)—correlation between prenatal and postnatal exposure. Chemosphere. 2004;54(10):1459–73.
74. Suzuki G, Nakano M, Nakano S. Distribution of PCDDs/PCDFs and Co-PCBs in human maternal blood, cord blood, placenta, milk, and adipose tissue: dioxins showing high toxic equivalency factor accumulate in the placenta. Biosci Biotechnol Biochem. 2005;69(10):1836–47.
75. Fletcher T, Steenland K, Savitz D. 2009. Status Report: PFOA and Immune Biomarkers in Adults Exposed to PFOA in Drinking Water in the Mid Ohio Valley: [http://www.c8sciencepanel.org/pdfs/Status_Report_C8_and_Immune_markers_March2009.pdf] (Accessed 27 Sept 2011).
76. Harada K, Koizumi A, Saito N, Inoue K, Yoshinaga T, Date C, et al. Historical and geographical aspects of the increasing perfluorooctanoate and perfluorooctane sulfonate contamination in human serum in Japan. Chemosphere. 2007;66(2):293–301.
77. Jensen AA, Leffers H. Emerging endocrine disrupters: perfluoroalkylated substances.

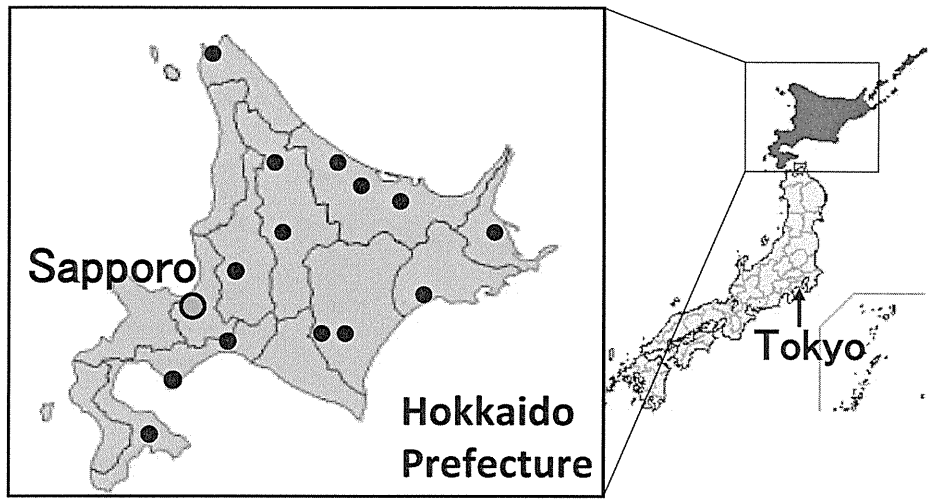
Int J Androl. 2008;31(2):161–9.

78. Kannan K, Corsolini S, Falandysz J, Fillmann G, Kumar KS, Loganathan BG, et al. Perfluorooctanesulfonate and related fluorochemicals in human blood from several countries. Environ Sci Technol. 2004;38(17):4489–95.
79. Yoshioka W, Peterson RE, Tohyama C. Molecular targets that link dioxin exposure to toxicity phenotypes. J Steroid Biochem Mol Biol. 2011;127(1–2):96–101.
80. Tsuchiya Y, Nakajima M, Yokoi T. Cytochrome P450-mediated metabolism of estrogens and its regulation in human. Cancer Lett. 2005;227(2):115–24.
81. Sørensen M, Autrup H, Møller P, Hertel O, Jensen SS, Vinzents P, et al. Linking exposure to environmental pollutants with biological effects. Mutat Res Rev Mutat Res. 2003;544(2–3): 255–71.
82. Braimoh TS. Effects of maternal secondhand smoke exposure and gene polymorphisms of CYP1A1, EPHX1 and NAT2 on infant birth size. Doctoral thesis. Japan: Hokkaido University; 2012.
83. Damstra T, Barlow S, Bergman A, Kavlock R, Kraak Glen V. Global assessment of the state-of the science of endocrine disruptors. Geneva: World Health Organization; 2002.
84. Aschim EL, Nordenskjold A, Giwercman A, Lundin KB, Ruhayel Y, Haugen TB, et al. Linkage between cryptorchidism, hypospadias, and GGN repeat length in the androgen receptor gene. J Clin Endocrinol Metab. 2004;89(10):5105–9.
85. Thai HT, Kalbasi M, Lagerstedt K, Frisen L, Kockum I, Nordenskjold A. The valine allele of the V89L polymorphism in the 5-alpha-reductase gene confers a reduced risk for hypospadias. J Clin Endocrinol Metab. 2005;90(12):6695–8.
86. Radpour R, Rezaee M, Tavasoly A, Solati S, Saleki A. Association of long polyglycine tracts (GGN repeats) in exon 1 of the androgen receptor gene with cryptorchidism and penile hypospadias in Iranian patients. J Androl. 2007;28(1):164–9.
87. Lichtenstein P, Carlstrom E, Rastam M, Gillberg C, Anckarsater H. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. Am J Psychiatry. 2010;167(11):1357–63.
88. Ikeno T, Kobayashi S, Baba T, Kishi R. Literature review of the prevalence of attention-deficit hyperactivity disorder (ADHD) and its relation to environmental factors (ADHD no yuubyouritsu to youiku kankyou ni kansuru bunken review). Hokkaido J Public Health. 2011;25(2):53–9 (in Japanese).
89. Strang-Karlsson S, Raikkonen K, Pesonen AK, Kajantie E, Paavonen EJ, Lahti J, et al. Very low birth weight and behavioral symptoms of attention deficit hyperactivity disorder in young adulthood: The Helsinki study of very-low-birth-weight adults. Am J Psychiatry. 2008;165(10):1345–53.
90. Wolke D, Samara M, Bracewell M, Marlow N, Group EPS. Specific language difficulties and school achievement in children born at 25 weeks of gestation or less. J Pediatr. 2008;152(2): 256–62.
91. Hille ETM, den Ouden AL, Saigal S, Wolke D, Lambert M, Whitaker A, et al. Behavioural problems in children who weigh 1000 g or less at birth in four countries. Lancet. 2001;357(9269): 1641–3.
92. Hack M, Youngstrom EA, Cartar L, Schluchter M, Taylor HG, Flannery D, et al. Behavioral outcomes and evidence of

psychopathology among very low birth weight infants at age 20 years. Pediatrics. 2004;114(4):932–40.

93. Hackett JA, Surani MA. DNA methylation dynamics during the mammalian life cycle. Philos Trans R Soc Lond B Biol Sci. 2013;368(1609):20110328.
94. Azumi K, Kobayashi S, Kishi R. Review: epigenetic research for the elucidation of the transgenelational effects of the environmental chemicals (Kankyou-kagaku bussitu no jisedaieikyou no kaimei ni okeru epigenetics kenkyuu). Hokkaido J Public Health. 2012;26(2):26–38 (in Japanese).
95. Baccarelli A, Bollati V. Epigenetics and environmental chemicals. Curr Opin Pediatr. 2009;21(2):243–51.
96. Bollati V, Baccarelli A. Environmental epigenetics. Heredity (Edinb). 2010;105(1):105–12.
97. Murphy SK, Adigun A, Huang Z, Overcash F, Wang F, Jirtle RL, et al. Gender-specific methylation differences in relation to prenatal exposure to cigarette smoke. Gene. 2012;494(1):36–43.
98. Hoyo C, Fortner K, Murtha AP, Schildkraut JM, Soubry A, Demark-Wahnefried W, et al. Association of cord blood methylation fractions at imprinted insulin-like growth factor 2 (IGF2), plasma IGF2, and birth weight. Cancer Causes Control. 2012;23(4):635–45.
99. Vrijheid M, Casas M, Bergstrom A, Carmichael A, Cordier S, Eggesbo M, et al. European birth cohorts for environmental health research. Environ Health Perspect. 2012;120(1):29–37.

Fig. 1 The geographical distributions of the collaborating hospitals in Hokkaido, Japan. The large circled dot indicates Sapporo city (the prefectural capital of Hokkaido). The black dots indicate the geographical distributions of the collaborating hospitals and clinics outside of Sapporo City



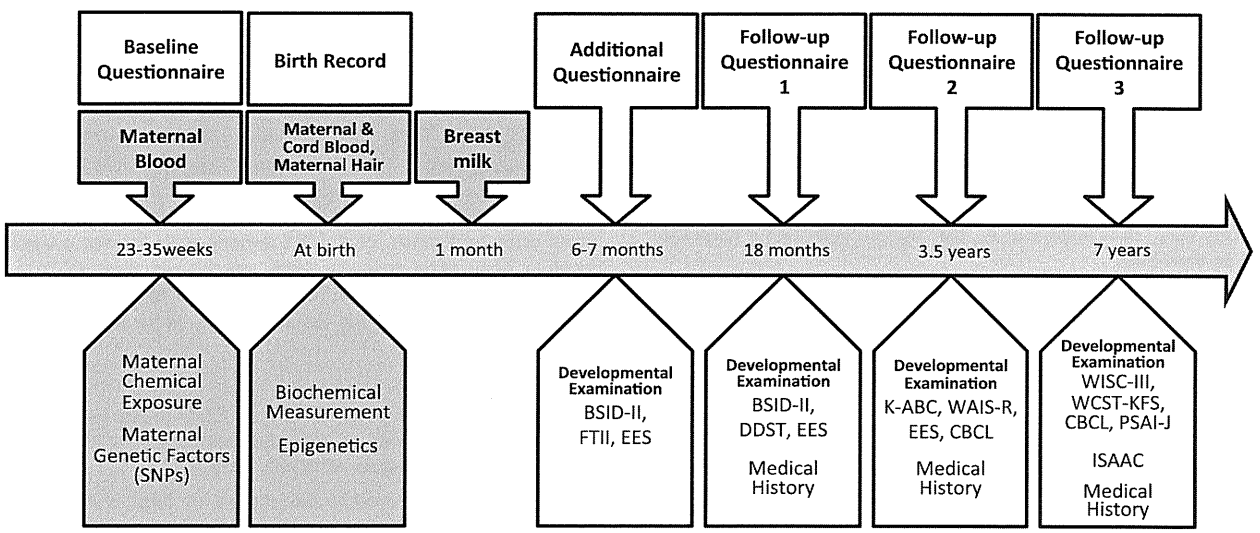


Fig. 2 Design of the Sapporo Toho hospital cohort study: obtaining information and specimens. SNPs single nucleotide polymorphisms, BSID-II The Bayley Scales of Infant Development-Second edition, FTII The Fagan Test of Infant Intelligence, EES the evaluation of environmental stimulation, DDST The Denver developmental screening tests, K-ABC The Kaufman-Assessment Battery for Children, WAIS-R The Wechsler Adult Intelligence Scale-Revised, CBCL Child Behavior Checklist, WISC-III The Wechsler Intelligence Scale for Children-Third edition, WCST-KFS Wisconsin Card Sorting Test-Keio-F-S version, PSAI-J Pre-School Activities Inventory-Japanese version, ISAAC International Study of Asthma and Allergies in Childhood

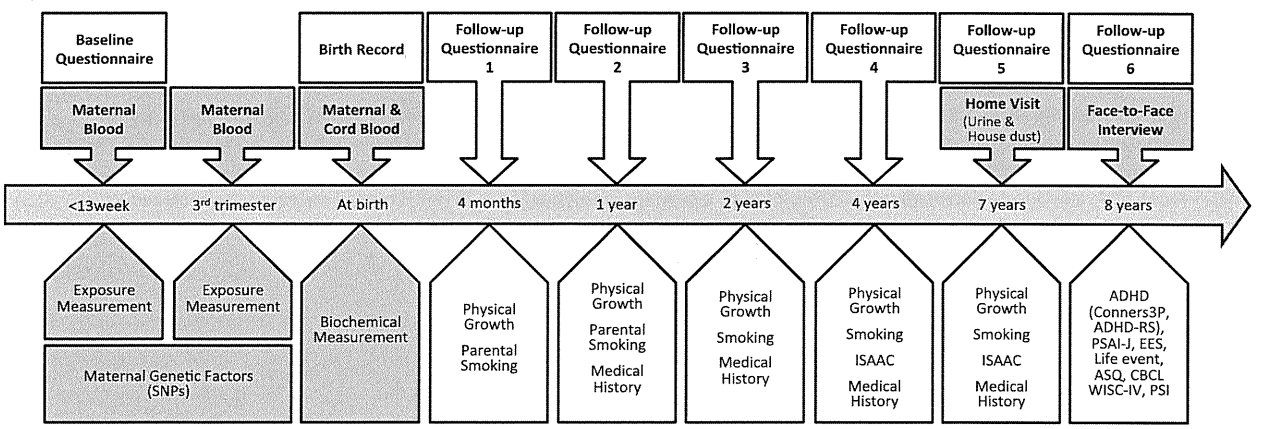


Fig. 3 Design of the Hokkaido large-scale cohort study: obtaining information and specimens. SNPs single nucleotide polymorphisms, ISAAC International Study of Asthma and Allergies in Childhood, ADHD attention deficit hyperactivity disorder, Conners3P The Conners Third edition Parent, ADHD-RS attention deficit hyperactivity disorder-rating scale, PSAI-J Pre-School Activities Inventory-Japanese version, EES the evaluation of environmental stimulation, Life Event life event questionnaire for parents, ASQ autism screening questionnaire, CBCL child behavior checklist, WISC-IV The Wechsler Intelligence Scale for Children-Fourth edition, PSI Parenting Stress Index

Table 1 Items measured in the Hokkaido study on environment and children's health

Specimen	Measurement
Exposure measurement	
Maternal blood	PCB and dioxin; PCDD and PCDF (congeners)
	OH-PCB (congener level)
	PFCs (PFOS, PFOA and other PFAAs)
	MEHP (phthalate metabolite)
	Chlorinated pesticides
	Cotinine
Maternal hair	Me-Hg
Cord blood	BPA
Child urine	Cotinine
	Phthalate and phosphate esters (7-year-old)
House dust	Phthalate and phosphate esters (7-year-old)
Biochemical measurements	
Maternal blood	TSH, FT4, Folic acid, 11 Fatty acids
Cord blood	IgE, TSH, FT4, 9 Steroid hormones

PCB polychlorinated biphenyls, PCDF polychlorinated dibenzofurans, PCDD polychlorinated dibenzodioxins, OH-PCB hydroxylated polychlorinated biphenyl, PFCs perfluorinated compounds, PFOS perfluorooctane sulfonate, PFOA perfluorooctanoic acid, PFAAs perfluoroalkyl acids, MEHP mono-2-ethylhexyl phthalate, Me-Hg methylmercury, BPA bisphenol A, TSH thyroid stimulating hormone, FT4 free thyroxine

Table 3 Gender differences in the effect of PCB/dioxins exposure on birth weight in a multiple linear regression model

$\log_{10}$ scale	Male		Female	
	b[a]	p value	b[a]	p value
Total (pg/g lipid)				
Total PCDDs	− 125.7	0.371	− 19.3	0.890
Total PCDFs	− 237.6	0.191	− 304.9	0.058
Total PCDDs/PCDFs	− 136.6	0.340	− 28.7	0.839
Total non-ortho PCBs	− 90.7	0.491	− 122.4	0.286
Total mono-ortho PCBs	− 138.6	0.244	− 104.3	0.315
Total DL-PCBs	− 138.7	0.245	− 105.3	0.311
Total dioxin	− 148.5	0.229	− 106.8	0.319
TEQ (WHO 2005) (TEQ pg/g lipid)				
Total PCDDs TEQ	− 331.4	0.019*	− 126.3	0.336
Total PCDFs TEQ	− 269.8	0.070	− 241.7	0.058
Total PCDDs/PCDFs TEQ	− 338.7	0.022*	− 173.9	0.195
Total non-ortho PCBs TEQ	− 107.3	0.288	− 114.8	0.196
Total mono-ortho PCBs TEQ	− 138.6	0.244	− 104.3	0.315
Total DL-PCBs TEQ	− 112.1	0.278	− 117.5	0.195
Total dioxin TEQ	− 289.5	0.037*	− 144.2	0.243

This table was reconstructed by using data from a previously published study by Konishi et al. [59]. Among male infants, a significant negative association between birth weight and total PCDDs TEQ levels, total PCDDs/PCDFs TEQ levels and total TEQ levels was found. However, among the female infants, these significant associations were not found

* p¥ 0.05

The Toxicity Equivalency Quantity (TEQ) levels were calculated by multiplying the levels of individual congeners by its toxic equivalency factor (TEF) values of WHO 2005 [38]

[a] Beta coefficients represent the change in birth weight (g) for a 10-fold increase in the levels of PCDDs/PCDFs and DL-PCBs

Table 2 Genetic factors and its environmental interaction being studied in the Hokkaido study (up to 2013)

Maternal genetic factors	Environmental exposure	Outcomes	Results	Ref.
AHR, AHRR, CYP1A1, CYP1A2, CYP1B1	Dioxin and dioxin-like PCBs	(Concentration)	Decreased	[55]
AHR, CYP1A1, GSTM1, GSTT1	Active tobacco smoking (PAHs)	Birth size	Reduction	[56]
NQO1, CYP2E1, MGMT	Active tobacco smoking	Birth size	Reduction	[57]
5,10-MTHFR (C677T, A1298C)	Tobacco smoking and Folic acid	Birth weight	Reduction	[58]

Genes described in bold font in the table represent the genetic polymorphisms that are significantly associated with the outcome

AHR aryl hydrocarbon receptor, AHRR AHR repressor, CYP1 cytochrome P450, family 1, CYP1A1 CYP1 subfamily A polypeptide 1, CYP1A2 CYP1 subfamily A polypeptide 2, CYP1B1 CYP1 subfamily B polypeptide 1, GSTM1 glutathione-S-transferase mu-1, GSTT1 glutathione-S-transferase theta-1, NQO1 NAD(P)H: quinone oxidoreductase 1, CYP2E1 CYP2 subfamily E polypeptide 1, MTHFR methylenetetrahydrofolate reductase

Table 4 Gender differences in the effect of PCB/dioxins exposure on BSID-II Mental (MDI) and Psychomotor (PDI) development scores at 6 months of age in multiple linear regression models

(log_{10} transformed)	6 months MDI						6 months PDI					
	Male (n = 99)			Female (n = 91)			Male (n = 99)			Female (n = 91)		
	b[a]	t	p value	b[a]	t	p value	b[a]	t	p value	b[a]	t	p value
PCDD												
2,3,7,8-TCDD	−0.15	−1.54	0.13	−0.05	−0.48	0.63	−0.19	−2.01	0.048*	−0.06	−0.56	0.58
1,2,3,7,8-PeCDD	−0.07	−0.70	0.48	0.22	2.14	0.04*	−0.10	−0.98	0.33	−0.04	−0.33	0.75
1,2,3,4,6,7,8-HpCDD	−0.25	−2.52	0.01*	−0.14	−1.34	0.18	−0.24	−2.56	0.01*	−0.19	−1.78	0.08
OCDD	−0.09	−0.92	0.36	−0.18	−1.74	0.09	−0.22	−2.33	0.02*	−0.21	−1.97	0.05
PCDF												
2,3,7,8-TCDF	−0.08	−0.84	0.41	−0.11	−1.05	0.30	−0.21	−2.21	0.03*	−0.13	−1.21	0.23
1,2,3,7,8-PeCDF	−0.02	−0.22	0.83	−0.06	−0.54	0.59	−0.22	−2.38	0.02*	−0.17	−1.59	0.12
1,2,3,4,7,8-HxCDF	−0.07	−0.73	0.47	−0.10	−0.93	0.36	−0.17	−1.69	0.09	−0.25	−2.36	0.02*
Non-ortho PCB												
$3^{0}4^{0}5$-PenCB (#126)	−0.03	−0.33	0.74	−0.01	−0.10	0.93	−0.15	−1.62	0.11	−0.24	−2.25	0.03*
Mono-ortho PCB												
$234^{0}5$-PeCB (#114)	−0.07	−0.71	0.48	0.08	0.79	0.43	−0.19	−2.00	0.049*	−0.16	−1.49	0.14
$2^{0}34^{0}5$-PeCB (#123)	0.02	0.23	0.82	0.01	0.05	0.96	−0.13	−1.39	0.17	−0.25	−2.37	0.02*
$233^{0}4^{0}5^{0}$-HxCB (#157)	−0.08	−0.85	0.40	0.10	0.90	0.37	−0.21	−2.19	0.03*	−0.11	−1.09	0.28
$23^{0}4^{0}5^{0}5^{0}$-HxCB (#167)	−0.05	−0.49	0.63	0.04	0.41	0.69	−0.22	−2.35	0.02*	−0.15	−1.38	0.17
Di-ortho PCB												
$22^{0}33^{0}4^{0}5$-HpCB(#170)	−0.13	−1.25	0.22	0.10	0.88	0.38	−0.25	−2.47	0.02*	−0.04	−0.37	0.71
$22^{0}34^{0}5^{0}5^{0}$-HpCB(#180)	−0.13	−1.23	0.22	0.10	0.88	0.38	−0.24	−2.42	0.02*	0.00	0.01	1.00
Total												
Total PCDD	−0.10	−1.00	0.32	−0.17	−1.63	0.11	−0.22	−2.31	0.02*	−0.21	−1.97	0.05
Total PCDF	−0.06	−0.61	0.55	0.02	0.15	0.88	−0.18	−1.81	0.07	−0.20	−1.83	0.07
Total PCDD/PCDF	−0.10	−1.00	0.32	−0.17	−1.58	0.12	−0.22	−2.33	0.02*	−0.21	−1.98	0.05
Total non-ortho PCBs	−0.01	−0.12	0.91	0.03	0.25	0.81	−0.16	−1.72	0.09	−0.19	−1.73	0.09
Total mono-ortho PCBs	−0.05	−0.55	0.58	0.05	0.46	0.64	−0.19	−1.97	0.05	−0.17	−1.60	0.11
Total DL-PCB	−0.05	−0.55	0.59	0.05	0.46	0.65	−0.19	−1.97	0.05	−0.17	−1.60	0.11
Total dioxins	−0.06	−0.56	0.58	0.04	0.39	0.70	−0.19	−2.03	0.045*	−0.17	−1.65	0.10
Total PCDD-TEQ	−0.09	−0.87	0.39	0.14	1.31	0.19	−0.12	−1.24	0.22	−0.08	−0.77	0.44
Total PCDF-TEQ	−0.03	−0.28	0.78	0.08	0.73	0.47	−0.17	−1.74	0.09	−0.15	−1.42	0.16
Total PCDD/PCDF-TEQ	−0.08	−0.75	0.45	0.13	1.19	0.24	−0.14	−1.39	0.17	−0.10	−0.95	0.34
Total non-ortho PCBs-TEQ	−0.03	−0.28	0.78	0.01	0.08	0.94	−0.16	−1.67	0.10	−0.22	−2.04	0.04*
Total mono-ortho PCBs-TEQ	−0.05	−0.55	0.58	0.05	0.46	0.64	−0.19	−1.97	0.05	−0.17	−1.60	0.11
Total DL-PCB-TEQ	−0.05	−0.55	0.59	0.05	0.46	0.65	−0.19	−1.97	0.05	−0.17	−1.60	0.11
Total dioxins-TEQ	−0.05	−0.53	0.60	0.09	0.84	0.41	−0.15	−1.52	0.13	−0.15	−1.39	0.17

This table was constructed by reanalyzing the data from a previous study by Nakajima et al. [60]. Only statistically significant congeners are presented in this table (*p ¥ 0.05)

The TEQ levels were calculated by multiplying the levels of individual congeners by its TEF values of WHO 2005 [38]

Table 5 Gender differences in the effect of PCB/dioxins exposure on cord blood IgE level in multiple linear regression models

(log_{10} transformed)	Male (n = 112)				Female (n = 123)			
	Crude model		Adjusted model		Crude model		Adjusted model	
	b (95 % CI)	p value	b (95 % CI)	p value	b (95 % CI)	p value	b (95 % CI)	p value
Total								
Total PCDD	0.032 (− 0.681, 0.746)	0.928	− 0.061 (− 0.821, 0.700)	0.875	0.562 (− 0.164, 1.287)	0.128	0.594 (− 0.198, 1.386)	0.140
Total PCDF	− 0.630 (− 1.503, 0.244)	0.156	− 1.097 (− 2.127, − 0.067)	0.037**	0.455 (− 0.350, 1.261)	0.265	0.590 (− 0.313, 1.493)	0.198
Total PCDD/PCDF	0.012 (− 0.715, 0.740)	0.973	− 0.088 (− 0.866, 0.689)	0.822	0.571 (− 0.164, 1.306)	0.127	0.607 (− 0.195, 1.410)	0.136
Total non-ortho PCBs	− 0.201 (− 0.811, 0.410)	0.516	− 0.587 (− 1.305, 0.132)	0.108	0.383 (− 0.154, 0.919)	0.16	0.479 (− 0.110, 1.067)	0.110
Total mono-ortho PCBs	− 0.252 (− 0.804, 0.299)	0.367	− 0.482 (− 1.137, 0.172)	0.147	0.120 (− 0.366, 0.605)	0.626	0.230 (− 0.330, 0.790)	0.418
Total DL-PCB	− 0.253 (− 0.805, 0.300)	0.367	− 0.484 (− 1.140, 0.171)	0.146	0.121 (− 0.365, 0.607)	0.622	0.232 (− 0.329, 0.792)	0.415
Total dioxins	− 0.246 (− 0.817, 0.325)	0.395	− 0.521 (− 1.275, 0.234)	0.174	0.142 (− 0.346, 0.631)	0.566	0.375 (− 0.219, 0.970)	0.214
TEQ (WHO 2005)								
Total PCDD TEQ	− 0.630 (− 1.288, 0.028)	0.060*	− 1.008 (− 1.822, − 0.194)	0.016**	0.138 (− 0.453, 0.728)	0.645	0.332 (− 0.376, 1.039)	0.355
Total PCDF TEQ	− 0.689 (− 1.408, 0.030)	0.060*	− 1.229 (− 2.113, − 0.344)	0.007***	0.390 (− 0.227, 1.007)	0.213	0.643 (− 0.065, 1.352)	0.075
Total PCDD/PCDF TEQ	− 0.681 (− 1.373, 0.011)	0.054*	− 1.144 (− 2.006, − 0.282)	0.010**	0.203 (− 0.406, 0.812)	0.511	0.427 (− 0.299, 1.153)	0.246
Total non-ortho PCBs TEQ	− 0.234 (− 0.689, 0.222)	0.312	− 0.498 (− 1.017, 0.021)	0.060*	0.205 (− 0.216, 0.627)	0.337	0.251 (− 0.217, 0.719)	0.290
Total mono-ortho PCBs TEQ	− 0.252 (− 0.804, 0.299)	0.367	− 0.482 (− 1.137, 0.172)	0.147	0.120 (− 0.366, 0.605)	0.626	0.230 (− 0.330, 0.790)	0.418
Total DL-PCB TEQ	− 0.242 (− 0.708, 0.224)	0.305	− 0.514 (− 1.047, 0.019)	0.058*	0.202 (− 0.228, 0.632)	0.354	0.254 (− 0.224, 0.732)	0.295
Total dioxins TEQ	− 0.535 (− 1.176, 0.106)	0.101	− 1.011 (− 1.794, − 0.229)	0.012**	0.234 (− 0.337, 0.806)	0.419	0.406 (− 0.265, 1.076)	0.233

This table was reconstructed by using data from a previously published study by Washino et al. [61]. Multiple linear regression adjusted for mother's age, maternal allergy history, paternal allergy history, smoking during pregnancy, parity, gestational age, frequency of deep sea fish consumption, distance of highway to home and blood sampling period

* p¥ 0.10, ** p¥ 0.05, *** p¥ 0.01

The TEQ levels were calculated by multiplying the levels of individual congeners by their TEF values of WHO 2005 [38]

Table 6 Gender differences in the effect of PCB/dioxins exposure on the onset of otitis media at 18 months of age in multiple logistic regression models

(log_{10} transformed)		Adjusted			p-value for trend
		Quartile 2 OR (95 % CI)	Quartile 3 OR (95 % CI)	Quartile 4 OR (95 % CI)	
All					
TEQ					
PCDDs	P PCDDs	1.2 (0.53–2.7)	1.1 (0.50–2.6)	1.5 (0.65–3.5)	0.39
PCDFs	P PCDFs	1.6 (0.68–3.8)	2.2 (0.93–5.1)	2.5 (1.1–5.9)*	0.03
Non-ortho PCBs	P Non-ortho PCBs	1.8 (0.79–4.2)	2.5 (1.1–6.0)*	1.5 (0.62–3.6)	0.30
Total Dioxins		2.1 (0.92–4.8)	1.7 (0.71–3.9)	1.7 (0.70–4.1)	0.38
Congeners					
PCDDs	OCDD	3.4 (1.4–8.5)*	2.8 (1.1–7.0)*	2.6 (1.0–6.9)*	0.12
PCDFs	2,3,4,7,8-PeCDF	1.6 (0.7–3.9)	2.0 (0.88–4.8)	2.8 (1.2–6.6)*	0.02
Non-ortho PCBs	3,3',4,4'-TCB(#77)	2.4 (0.99–5.9)	1.4 (0.61–3.3)	3.4 (1.6–7.3)*	0.01
Mono-ortho PCBs	2,3,3',4,4',5-HxCB(#157)	2.4 (1.0–5.5)*	1.1 (0.43–2.7)	2.5 (1.1–5.9)*	0.16
Males					
TEQ					
PCDDs	P PCDDs	0.5 (0.13–1.8)	2.0 (0.65–6.2)	2.9 (0.83–10)	0.03
PCDFs	P PCDFs	1.0 (0.28–3.3)	2.9 (0.87–9.8)	3.8 (1.1–13)*	0.01
Non-ortho PCBs	P Non-ortho PCBs	2.4 (0.70–8.3)	2.9 (0.86–9.7)	3.6 (0.98–13.3)	0.05
Total dioxins		2.1 (0.61–6.9)	2.2 (0.67–7.1)	4.4 (1.2–16)*	0.03
Congeners					
PCDFs	2,3,4,7,8-PeCDF	1.7 (0.48–6.0)	2.9 (0.87–10)	5.3 (1.5–19)*	0.01
Non-ortho PCBs	3,3',4,4'-TCB(#77)	2.8 (0.85–9.4)	0.9 (0.24–3.4)	3.5 (1.2–11)*	0.08
	3,3',4,4',5,5'-HxCB(#169)	1.0 (0.25–3.8)	3.0 (0.93–9.6)	3.6 (1.1–12)*	0.01
Mono-ortho PCBs	2,3,4,4',5-PeCB(#114)	2.4 (0.62–8.9)	4.5 (1.2–16.6)*	4.9 (1.3–18)*	0.01
	2,3',4,4',5,5'-HxCB(#167)	3.1 (0.83–11)	3.3 (0.91–11)	3.7 (1.0–13)*	0.06
	2,3,3',4,4',5-HxCB(#157)	4.5 (1.2–17)*	1.6 (0.37–6.5)	7.5 (1.9–29)*	0.02
Female					
TEQ					
PCDDs	P PCDDs	2.3 (0.71–7.6)	0.5 (0.11–2.0)	1.1 (0.30–4.1)	0.44
PCDFs	P PCDFs	4.0 (1.1–14.7)*	1.2 (0.30–5.1)	1.3 (0.29–5.8)	0.41
Non-ortho PCBs	P Non-ortho PCBs	1.3 (0.41–4.3)	1.9 (0.51–7.1)	0.8 (0.22–3.1)	0.86
Total Dioxins		2.6 (0.78–8.6)	1.0 (0.25–4.0)	1.0 (0.27–4.1)	0.57
Congeners					
Non-ortho PCBs	3,3',4,4'-TCB(#77)	1.4 (0.3–6.9)	1.5 (0.45–4.9)	3.8 (1.2–12)*	0.03

This table was reconstructed by using data from a previously published study by Miyashita et al. [62]. Only statistically significant congeners are presented in this table. (* p¥ 0.05). The OR (95 % CI) versus the first quartile (reference) in the logistic regression model was adjusted for maternal educational level, parity, infant gender, duration of breast-feeding, environmental tobacco exposure, day care attendance and blood sampling period (infant gender was excluded from covariates in gender-stratified analysis)

[a] quartiles applied as ordinal variables in the model

* p¥ 0.05, ** p¥ 0.01; Statistically significant, p-value

The TEQ levels were calculated by multiplying the levels of individual congeners by its TEF values of WHO 2005 [38]

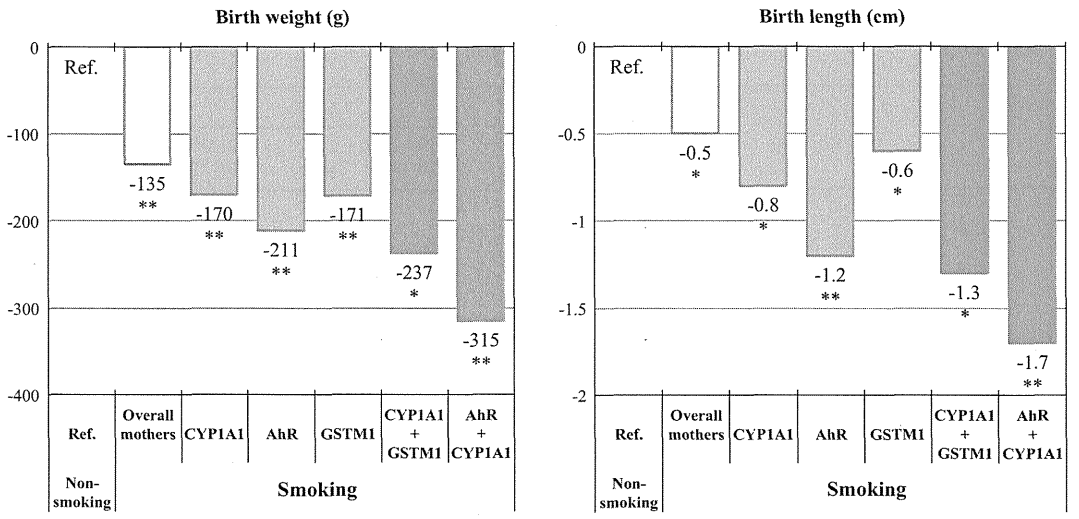


Fig. 4 The effects of maternal smoking in combination with maternal PAHs-metabolism-related genetic polymorphisms on infants' birth size. Adjusted for maternal age, height, weight before pregnancy, alcohol consumption during pregnancy, history of delivery, newborn sex, gestational weeks and household income. *p¥ 0.05, **p¥ 0.01 This figure was created by modifying a figure contained in our previous study by Sasaki et al. [56]

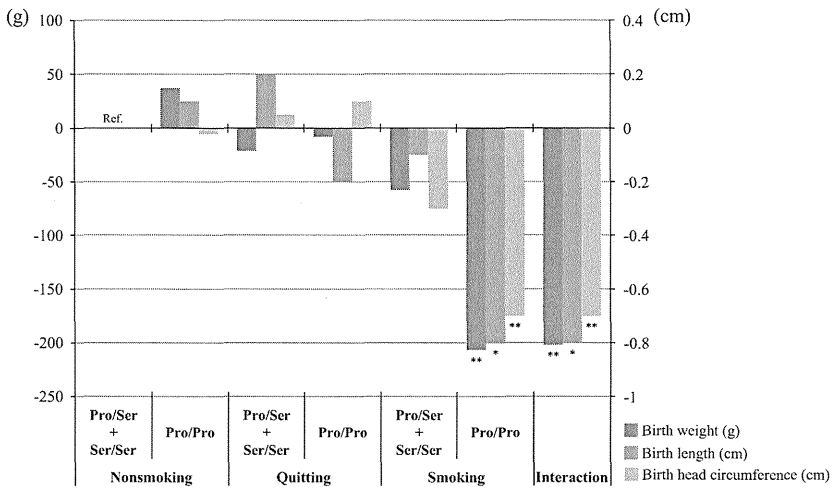


Fig. 5 The effects of maternal smoking in combination with maternal NQO1 genotype on infants' birth size. Adjusted for maternal age, height, weight before pregnancy, weight gain during pregnancy, alcohol consumption during pregnancy, parity, infant gender, gestational age, and household income. Interaction in multiple linear regression models was defined as product terms for the product of the dummy independent variables: maternal smoking status (nonsmoker, quitter or smoker) and genotype (wild or mutant). b represents the product term for smoker 9 wild genotype. NQO1 NAD(P)H: quinone oxidoreductase 1, Pro proline, Ser serine This figure was constructed by using the data from previous study by Sasaki et al. [57]

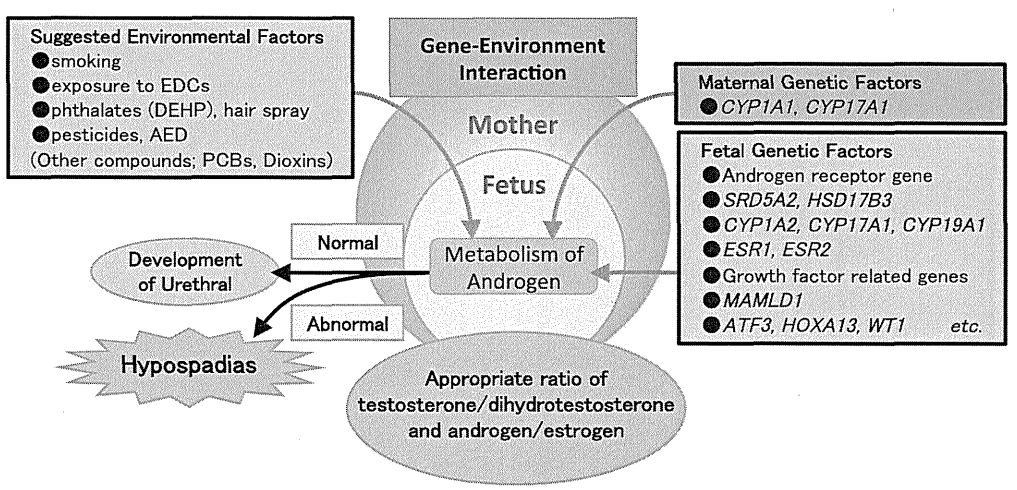


Fig. 6 Summary and suggestions for further studies on the environmental and genetic factors that influence hypospadias development. This figure was created by modifying a figure contained in our previous review by Kishi et al. [26]