Birth cohorts in Asia: The importance, advantages, and disadvantages of different-sized cohorts

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*Graphical Abstract

Highlights

- Birth cohorts in Asia can range from 100 to over 100,000 participants.
- Even small-sized cohort indicates association of low level dioxin exposure and child health.
- Several Asian cohorts focus on prenatal exposure to PFASs and various health outcomes.
- Large cohorts can target rare diseases, although need enormous research funds.
- BiCCA require harmonization of the exposure assessment and meta-analysis.

Abstract

Asia contains half of the world's children, and the countries of Asia are the most rapidly industrializing nations on the globe. Environmental threats to the health of children in Asia are myriad. Several birth cohorts were started in Asia in early 2000, and currently more than 30 cohorts in 13 countries have been established for study. Cohorts can contain from approximately 100-200 to 20,000-30,000 participants. Furthermore, national cohorts targeting over 100,000 participants have been launched in Japan and Korea. The aim of this manuscript is to discuss the importance of Asian cohorts, and the advantages and disadvantages of different-sized cohorts. As for case, one small-sized (n = 514) cohort indicate that even relatively low level exposure to dioxin *in utero* could alter birth size, neurodevelopment, and immune and hormonal functions. Several Asian cohorts focus prenatal exposure to perfluoroalkyo substances and reported assocations with birth size, thyroid hormone levels, allergies and neurodevelopment. Inconsistent findings may possibly be explained by the differences in exposure levels and target chemicals, and by possible statistical errors. In a smaller cohort, novel hypotheses or preliminary examinations are more easily verifiable. In larger cohorts, the etiology of rare diseases, such as birth defects, can be analyzed; however, they require a large cost and significant human resources. Therefore, conducting studies in only one large cohort may not always be the best strategy. International collaborations, such as the Birth Cohort Consortium of Asia, would cover the inherent limitation of sample size in addition to heterogeneity of exposure, ethnicity, and

socioeconomic conditions.

1. Introduction: Importance of birth cohorts in Asia

In 1997, Colborn et al. published the book “Our Stolen Future: Are We Threatening Our Fertility, Intelligence, and Survival?” (Colborn et al. 1997), which warned of the dangers of environmental chemicals as endocrine disruptors. Since then, concern of the impact of environmental chemicals that could lead to impaired reproductive capacity has become a global interest. The World Health Organization (WHO) and International Programme on Chemical Safety published the report “Global Assessment of the State-of-the-Science of Endocrine Disruptors“ in 2002 (IPCS 2002), which has been updated as “State of the Science of Endocrine Disrupting Chemicals - 2012” by the WHO and United Nations Environment Programme (UNEP and WHO 2012). WHO Headquarters also published “Endocrine Disrupting Chemicals and child health: Possible developmental early effects of endocrine disrupters on child health,” which compiles the existing evidence (WHO 2012).

Historically, many epidemiological studies have been conducted in Europe. One of the oldest cohort, which examined environmental chemical exposure, is in Faeroe Island; they started their enrollment in mid-1980, and there were 1,022 singleton births (Weihe and Grandjean, 2012). In 2009, birth cohorts gathered and established projects such as the Environmental Health Risks in European Birth Cohorts within the European Union’s 7th Framework Program. It aims to advance knowledge on the relationships between specific environmental factors and health in pregnancy and birth cohorts by providing support to utilize the wealth of data generated by past and ongoing studies funded by the

European Union and national programs (Vrijheid et al. 2012).

On the other hand, Asia contains half of the world's children, and the countries of Asia are the most rapidly industrializing nations on the globe. Environmental threats to the health of children in Asia are myriad. In Asia, several birth cohorts were launched in early 2000. The Birth Cohort Consortium of Asia (BiCCA) was co-established in 2011 by the principal investigators of three birth cohorts in Asia: the Taiwan Birth Panel Study (TBPS), the Mothers and Children's Environmental Health Study (MOCEH, Korea), and the Hokkaido Study on Environment and Children's Health (The Hokkaido Study, Japan) (Kishi et al. 2017). The primary aims of BiCCA are 1) to facilitate exchange of knowledge and collaboration between cohorts and researchers, and 2) exploration of the future needs of children's environmental health research. As of April 2017, 27 cohorts in 13 countries have joined the BiCCA project (Table 1), and they are quite diverse in study area. The number of participants in each cohort ranges from small (100–3,000) to medium (more than 3,000 to 10,000), and large (more than 10,000). Furthermore, the Ministry of Environment, Government of Japan launched the Japan Environment and Children's Study (JECS) in 2011, and successfully recruited a large number of participants consisting of 100,000 parent-child pairs (Kawamoto et al., 2014). The Korean Children's Environmental Health Study (Ko-CHENS!) has been recruiting pregnant women since 2015, targeting 100,000 participants (Ha et al. 2016); therefore, larger cohorts may be paid more attention.

Birth cohorts that come from a local area issue are important. Environmental threats to the

health of children in Asia are diverse, and include classic infectious disease hazards. Several BiCCA cohorts, including those in China, Korea, Mongolia, Singapore, and Taiwan, focus on outdoor air pollution, such as smog, sandstorms, and haze, which are not only regional but trans-boundary threats (B. M. Kim et al. 2009; Kishi et al. 2016; Kishi et al., 2017; Bae et al, 2017; Soh et al. 2014; Wen et al. 2011; Yang et al. 2014). Heavy metals are also a local area issue. Fish consumption is a risk for dioxins, PCBs, and methyl mercury that has been a focus in China, Japan, Korea, and Taiwan (Bae et al. 2017; Gao et al. 2016; Hsieh et al. 2011; B. M. Kim et al. 2009; Kishi et al. 2017; Kishi et al., 2016; Kishi et al. 2013; Kishi et al. 2011; Nakai et al. 2004; Y. Wang et al. 2014; Wen et al. 2011), whereas high arsenic is an issue in Bangladesh (Kile et al. 2016). The increasing number of overweight and obese individuals is another growing issue. The majority of studies have been conducted in measuring birth size, although the Malaysia cohort has examined biomarkers together with anthropometric measurements (Loy and Hamid Jan 2014). Although the sample size of these cohorts is smaller than the large scale nation-wide cohorts, they have contributed both novel findings and preventive measures; therefore, the significance of the small cohort should not be ignored.

The aim of this manuscript is to discuss the importance, the advantages and disadvantages of different-sized cohorts in Asia, while showing representative findings. In this manuscript, we have focused on and summarize the persistent organic pollutants, such as dioxins and perfluoroalkyl substances (PFASs) . Recently, environmental chemicals with short half-lives, such as phthalate esters,

and bisphenols have also been a concern, as humans are exposed to these chemicals ubiquitously. These chemicals require exposure assessment; however, exposure to which chemicals or metabolites, when, how many times, etc. should also be discussed in a separate manuscript.

2. Dioxin exposure in Asian countries

Dioxins are a group of chemical compounds that are persistent environmental pollutants. Polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like polychlorinated biphenyls (DL PCBs) have human health effects that have become distributed in environments worldwide (Kogevinas, 2001). Yusho and Yucheng are oil diseases that occurred because of ingestion of accidentally contaminated rice oil in the western part of Japan in 1968 (PCDD/PCDFs and dioxin-like PCBs in blood level: 215.4 pg/g TEQ lipid) (Yoshimura 2003) and in Taiwan in 1978-1979 (PCDD/PCDFs in blood level: 6550 pg/g TEQ lipid) (Guo et al. 2004). During the Vietnam War from 1961 to 1972, herbicides contaminated with 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), the most toxic congener of dioxin, was sprayed in Southern Vietnam area. Because of the extremely high levels of TCDD in the soil samples at military airbases formerly used for storing herbicides, these areas were characterized as “hot spots” of TCDD contamination (TCDD in breast milk: 1,832 pg/g lipid) (A Schecter et al., 1995). The dioxin levels in breast milk of lactating mothers in the hot spots were reported to be approximately 4-fold higher than those of lactating mothers

residing in unsprayed areas four decades after the herbicide spraying (PCDD/PCDFs in breast milk: 14.1 pg/g TEQ lipid in hot spot vs 4.1 in unsprayed areas) (Tai et al. 2011). Thus, several cohort studies in Vietnam have focused on the residents around these hot spots and the second generation exposed to high levels of dioxins (Kido et al. 2014; Nishijo et al. 2012).

The general population that had no history of accidental poisonings or currently live in a non-contaminated area had relatively lower exposure levels compared to those who were exposed to high levels due to accidental poisonings. Neverthless, the general population is continually exposed to dioxins via consumption of daily food intake. Environmental exposure levels of dioxins were compared with other countries and regions as shown in Figure 1. The median or mean concentrations of PCDD, PCDF, and DL PCB) toxic equivalents (TEQs) in breast milk for the collection period from 1999 to 2004 in Asian countries such as Hokkaido and Tohoku in Japan, China, Korea, and Taiwan, were relatively lower than those in Europe [the Netherlands, Italy, and Germany] or the US (Nakamura et al. 2008; Nakatani et al. 2005; Todaka et al. 2010).

2.1. Dioxins hazard assessment with a small-sized cohort: Sapporo Cohort

Alteration of even relatively low level dioxin exposure on infant health of the next generation was not well understood. A few human studies have addressed prenatal exposure to low environmental levels of PCDDs/PCDFs and DL-PCBs. The following is example of a small sample cohort, the Sapporo

128 cohort, examined the effects of dioxin exposure on adverse fetal health outcomes. The case shows how
129 novel hypotheses or trials are easily verifiable in a small cohort. The Sapporo cohort enrolled 514
130 pregnant women at one hospital in Sapporo, Japan in 2002-2005. Detailed information can be found
131 in our cohort profiles (Kishi et al. 2017; Kishi et al. 2013; Kishi et al. 2011). The cohort focused on
132 child neurodevelopment, allergies and infectious diseases, and endocrine and metabolism disorders.
133 They assessed rigorous and congener level measurements of dioxins, DL-PCBs, other PCBs, and
134 hydroxylated PCBs (Todaka et al. 2007, 2008a; Todaka et al. 2008b).

135 Although maternal exposure levels of dioxin like compounds (DLCs) in the Sapporo cohort
136 were relatively lower than that in Europe and the US, adverse effects of prenatal exposure to DLCs on
137 offspring health were observed in this cohort (Table 2). These effects include reduced birth weight
138 (Konishi et al. 2009), reduced IgE at birth (Washino et al. 2007), increased free thyroxine (T4) (Baba
139 et al., 2012), delay of neurodevelopment at 6 months (Nakajima et al. 2006), increased risk of
140 infections at 18 months of age (Miyashita et al. 2011), and increased risk of wheeze at 7 years old
141 (Miyashita et al. 2017). In specific congener analysis, maternal 2,3,4,7,8-pentachlorodibenzo-furan, a
142 PCDF congener, was associated with decreased child birth weight (per log 10 unit: β = -24.5 g; 95%
143 CI: -387.4–-61.5) (Konishi et al 2009) and increased risk of otitis media (OR: 5.3; 95% CI: 1.5–19)
144 (Miyashita et al. 2011). The maternal PCDD isomer 1,2,3,4,6,7,8-HpCDD was negatively associated
145 with mental developmental index (MDI) in children at 6 months of age. Four maternal PCDD isomers

and one PCDF isomer were negatively associated with psychomotor developmental index (PDI) in children at 6 months of age (Nakajima et al. 2006). On the other hand, at 18 months of age, the associations observed at 6 months had almost disappeared (Nakajima et al. *in press*). At age 3.5 years, the Mental Processing Composite Score of the Kaufman Assessment Battery for Children showed almost no relationship with maternal levels of DLCs, but did show a significant negative relation with one PCDF isomer, 2,3,4,6,7,8-HxCD (Ikeno et al. submitted to this STOTEN special issue). In the Sapporo cohort, associations between higher levels of DLCs and any of the outcomes examined, including birth weight, cord blood IgE, risk of infectious diseases, and delay of neurodevelopment at early life, were all found in male infants, suggesting that boys were more susceptible to DLCs than girls (Kishi et al., 2013). Their effects on steroid and reproductive hormones at birth and follow-up at onset of puberty are now being examined. DLCs are highly resistant to biodegradation in the environment; for example, the estimated half-life of TCDD is 7-8 years (Kogevinas, 2001). Although the sample size is relatively small, results from the Sapporo cohort, clearly indicated that the effects of prenatal exposure, even at the relatively low DLC levels in Sapporo, Japan compared to other areas in the world, could cause various health outcomes in offspring.

3. PFASs health hazard assessment from different-sized cohorts in Asia

Another class of persistent organic compound (POP) that has drawn focus worldwide is the

PFASs. Although there have been a variety of environmental contaminant health hazard assessed in each cohort in Asia, here we focus on PFASs exposure and their effects. PFASs are used in a broad range of consumer products because of their surface properties. Since 2009, perfluorooctanesulfonic acid (PFOS) have been included in Annex B of the Stockholm Convention on POPs (UNEP 2007). Tables 3 to 6 describe findings from Asian birth cohort studies till date.

3.1. Exposure levels

PFOS and perfluorooctanoate PFOA levels in maternal and cord samples of Asian, European and the North American countries are shown in Figure 2. Maternal levels of both PFOS and PFOA in Japan and Taiwan were at similar levels. (Okada et al. 2013; Washino et al. 2009, Wang et al. 2016). Maternal PFOS levels in Korea (Kim et al. 2011) were slightly lower compared to others. Cord levels of PFOS and PFOA measured in Korea (Y. J. Lee et al. 2013, Kim et al. 2011, Shah-Kulkarni et al. 2016), and in China (Li et al. 2017, Shi et al. 2017) were at the same range. On the other hand, cord PFOS and PFOA levels reported in Taiwan (Chen et al. 2012) were much higher than levels in Korea and China. Cord levels were lower compared to maternal levels (Kim et al. 2011), which was reasonable because 35% of the PFOS and 85% of the PFOA in cord blood is transferred from the maternal serum (Inoue et al. 2004; Y. J. Lee et al. 2013). The PFOS levels among Asian countries were in the similar range. Compared to the European countries and North American countries, the

182 levels may slightly lower, however, this could be due to differences in sampling periods. PFOA levels
183 of Asian, Europe and the North Americans were in the similar range. The sources of exposure, such as
184 drinking water, inhalation of indoor air, ingestion of house dust, direct contact with consumer products,
185 increased time periods with continuous use, and emissions, may contribute to the variability in levels
186 between these study areas (Fromme et al. 2009; Gyllenhammar et al. 2015; Haug et al. 2011).

187 Previously, the trends of 11 types of PFAS in maternal blood during 2003-2011 were
188 reported. The decrease in PFOS and PFOA, which has also been shown in different countries, could
189 be explained by limited use of these chemicals in recent years (Calafat et al. 2007; Okada et al. 2013;
190 Olsen et al. 2012; Olsen et al. 2008). Levels of perfluorononanoic acid (PFNA) and perfluorodecanoic
191 acid (PFDA), which have longer chains, were increasing (Okada et al. 2013). Similar increasing trends
192 were also found in the serum samples in Korea (Harada et al., 2011), as well as in the US and Europe
193 (Calafat et al. 2007; Glynn et al. 2012). It is worth noting that the detection rate for PFASs with longer
194 than 11 chains, such as perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA),
195 and perfluorotridecanoic acid (PFTrDA), was higher than 90% in Japan studies (Goudarzi et al. 2017;
196 Okada et al. 2014). There are few human studies focusing on the effects of long-chain PFASs on human
197 health; therefore, additional studies are needed to clarify the effects of these newly emergent chemicals
198 on human health, especially in Asia, where these long-chain PFASs are still being produced.
199

3.2. Birth weight and growth

In the past ten years, birth cohort studies have accumulated evidence on the associations between PFAS exposure and birth weight and birth size, as shown in Table 3. The majority of the studies have investigated PFOA and PFOS, two of the most widely used PFASs. Three studies from Asian countries showed that prenatal PFOS exposure was associated with reduced birth weight (Chen et al. 2012; Li et al. 2017; Washino et al. 2009). Furthermore, recently Li et al. reported that branched PFOS has a more significant association with reduced birth weight than does linear PFOS (Li et al. 2017). In addition to PFOS and PFOA, a study from Taiwan (Wang et al. 2016) reported that PFNA, PFDA, PFUnDA, and PFDoDA were associated with reduced birth weight in girls, and a study from Korea Lee et al. 2013) reported a significant inverse association between cord perfluorohexane sulfonate (PFHxS) concentration and birth weight. On the other hand, a recent study from China reported no significant associations between PFASs exposure and birth weight, birth length and ponderal index (Shi et al. 2017).

A meta-analysis of nine epidemiological studies worldwide showed that developmental exposure to PFOA may reduce fetal growth, specifically finding that a 1-ng/mL increase in serum or plasma PFOA in maternal/cord blood was associated with 18.9 g (95% CI: -29.8, -7.9) lower birth weight (Johnson et al. 2014). A systematic review including 14 studies concluded that *in utero* exposure to PFOA was associated with decreased birth weight in all studies, with and without

218 statistical significance (Bach et al. 2015). Similarly, maternal or cord blood PFOS levels were
219 inversely associated with birth weight in many studies, while some studies showed no association
220 (Bach et al. 2015). Of the Asian cohorts, the Sapporo cohort, the TBPS, and the Gyeongbuk province,
221 Korea are included in these systematic review, indicating that even small size cohorts had a significant
222 contribution.

223 In addition to PFOA and PFOS, other PFASs, including perfluoroheptanoic acid, PFNA,
224 PFDA, PFUnDA, and PFDoDA, have been investigated recently. We previously determined that
225 PFNA and PFDA levels increased between 2003 and 2011, while PFOS and PFOA concentrations
226 declined (Okada et al. 2013). Therefore, the association of birth weight and birth size with exposure
227 to these alternative PFASs should be examined.

228 Recently, not only birth weight, but also metabolic biomarkers such as adipokine levels in
229 cord blood samples have been investigated in association with PFAS exposure (Ashley-Martin et al.
230 2017; Fleisch et al. 2017; Minatoya et al. 2017a). Moreover, recent findings suggested that DNA
231 methylation related to fetal growth regulation (Kobayashi et al. 2016; Watkins et al. 2014) may be a
232 clue to fully elucidate the etiology of reduced birth weight and birth size via prenatal exposure to
233 PFASs. In these methylation studies, it has been suggested that large sample size is not necessarily
234 crucial.

235

3.3. Effects on thyroid hormones

There have been several reports in Asia from varied sample sizes (from 44 to 392) on the relationship between prenatal exposure to PFASs and the thyroid hormone levels of mothers and infants (Table 4). For maternal hormone analysis, the Taiwan Maternal and Infant Cohort Study (TMICS) reported that maternal PFHxS was positively associated with thyroid stimulating hormone (TSH), and PFNA, PFUnDA, and PFDoDA were inversely associated with free and total T4 levels in the third trimester (Y. Wang et al. 2014). The Sapporo cohort reported that maternal PFOS levels were inversely associated with maternal serum TSH during early gestation (Kato et al. 2016). Since values of maternal TSH at early gestational stage are suppressed by the elevation of human chorionic gonadotropin (hCG) levels, previous studies, including the TMICS, used the thyroid hormone data after the second trimester of pregnancy to avoid the effect of hCG. However, the disruption of maternal thyroid hormone levels at early gestational stages would be detrimental for not only maternal but also fetal health, because the fetus completely depends on the maternal hormone supply before fetal thyroid glands begin to secrete hormones.

Regarding the infants' thyroid hormones, the TBPS reported that cord blood PFOS was associated with higher TSH levels in the cord blood, especially in boys (Tsai et al. 2017). The TMICS found that PFNA, PFUnDA, PFDoDA, and PFDA in maternal serum were inversely associated with cord blood triiodothyronine (T3) and/or total T4 (Wang et al. 2014). In South Korea,

cord blood perfluoropentanoic acid (PFPeA) and PFHxS were associated positively with T4 and T3, while PFNA was inversely associated with TSH in girls (Shah-Kulkarni et al. 2016). Another Korean study reported that maternal PFOS was inversely associated with T3 in the cord blood, and maternal PFTrDA was positively associated with T3 and T4 in the cord blood (n = 44) (S. Kim et al. 2011). In the Sapporo cohort, maternal PFOS levels were positively associated with TSH by heel-prick blood in boys (Kato et al. 2016).

Some studies have been reported from European countries. The Northan Norway Mother-and-Child contaminant Cohort Study (The MISA study) reported that exposure to maternal PFOS, PFDA, and PFUnDA during pregnancy altered maternal and infant's thyroid hormone levels (Berg et al. 2017). The Linking EDCs in maternal Nutrition to Child health (LINC) study in the Netherlands found that high levels of PFOA were associated with high T4 in girls (de Cock et al. 2014).

These results are mainly consistent in Asia and Europe with those seen for PFASs, particularly as exposure to PFASs with carbon chains longer than 7 alters thyroid hormone levels in infants. In addition, these findings indicate that boys were more susceptible to longer chain PFAS exposure, while girls were more susceptible to shorter chain PFASs. However, the mechanism behind this gender difference is still unclear. Hormone values drastically change according to the stage of gestation, postnatal days, and delivery stress, such as labor pain, the duration of labor, and uterotonic agents. The somewhat inconsistent findings from previous studies may be because of

these differences; therefore, the accumulation of this vast evidence is a common concern worldwide, including Asia.

3.4. Allergies and infectious diseases

In Table 5, we have summarized the associations between PFASs and IgE, allergies, and infectious diseases. There are two cohorts in Asia examining the effect of PFOS and PFOA on IgE and allergies in similar small sample sizes. In the TBPS, Wang et al. (I. J. Wang et al. 2011) reported a positive correlation of PFOS and PFOA with cord blood IgE levels, and, after sex stratification, this correlation remained significant only in boys. Additionally, they did not observe an association between PFASs and atopic dermatitis. However, the Sapporo cohort reported that cord blood IgE level decreased significantly with high maternal PFOA, but not PFOS, levels in female infants. Additionally, there was no relationship observed in the Sapporo cohort between maternal PFOS and PFOA levels and infant allergies and infectious diseases at 18 months (Okada et al. 2012). These two small Asian cohorts have almost the same sample sizes, but contrasting results of the effects of PFASs on cord blood IgE levels. In the Taiwanese study, exposure assessment was conducted in cord blood; however, in the Sapporo cohort, prenatal PFAS levels were assessed, indicating lower exposure levels than those in the TBPS. The contrasting results may be partly explained by different exposure levels and applications.

290 A cohort (the Hokkaido large sized Cohort) examined not only PFOS and PFOA, but also
291 included longer carbon-chain PFASs. It was found that lower prenatal exposure to PFTrDA may
292 decrease the risk of eczema in infants in the first 2 years of life (Okada et al. 2014). When this
293 population was followed up at age 4, *in utero* exposure to long-chain PFASs, such as PFDoDA and
294 PFTrDA, was inversely associated with eczema and total allergic diseases (Goudarzi et al. 2016a).
295 On the other hand, PFHxS and PFOS were associated with increased risk of infections up to 4 years
296 of age (Goudarzi et al. 2017). These findings from a large–sized cohort but sample size was under
297 2000 for the follow-up observation period suggest that prenatal PFASs may have immunotoxic and
298 immunosuppressive effects in the next generation.
299 On the other hand, in the Faroe Islands, 587 mother-child pairs were followed up until the
300 children were 7 years of age, and PFASs during pregnancy and in 5-year old children were
301 examined. As outcomes, they examined serum antibody concentrations against tetanus and
302 diphtheria vaccines in 5- and 7-year-olds. PFAS levels in this study were 3-4 times higher than those
303 in the Sapporo cohort. Although the sample size of this study was not very big, the measurement of
304 pre- and postnatal PFASs along with the long follow-up period provided novel insights into the
305 reduced humoral immune response in children exposed to high PFAS levels. PFASs and post-natal
306 exposure to PFOS and PFOA were negatively associated with tetanus and diphtheria antibody levels
307 in 5- and 7-year-old children (Grandjean et al. 2012). In Norway, Granum et al. (2013) reported an

inverse association between prenatal PFASs and serum anti-rubella antibody levels in children at age 3 (Granum et al. 2013). They also observed a positive association between PFAS levels and the occurrence of the common cold and gastroenteritis in children. Furthermore, a Danish study showed that higher prenatal concentrations of PFOS and PFOA were associated with prevalence of fever as a marker of infections in early childhood (Dalsager et al. 2016).

3.5. Effects on neurodevelopment

Multiple studies have been conducted on prenatal exposure to PFASs and child neurobehavioral development. These epidemiological studies used various assessment tools at different age points. Additionally, focused outcomes were varied, from mental or motor development to IQ, or even symptoms such as Attention Deficit Hypertension Disorder (ADHD) or Autism Spectrum Disorder (ASD). Thus, findings from these studies seem to be inconsistent and not quite comparable to each other. Table 6 shows findings on PFAS exposure and child neurodevelopment and behavioral problems from Asian birth cohort studies. The concentrations of PFOS and PFOA were similar, with the exception of the TMICS, which showed a median PFOS concentration of 13.25 ng/mL (Y. Wang et al. 2015). The study populations were relatively small (< 300); however, three (Chen et al. 2013; Goudarzi et al. 2016a; Lien et al. 2016) out of four studies conducted face-to-face behavioral assessment of children by trained professionals, which provided more precise and detailed child

326 neurobehavioral developmental outcomes. From this point of view, small birth cohort studies seem to
327 be advantageous. In Europe, a nested case-control study in the Danish National Birth Cohort,
328 measurements of PFASs were conducted for 220 case of each ADHD and autism and matched controls
329 of 550, and found no consistent evidence to suggest that prenatal PFAS exposure increases the risk of
330 ADHD or childhood autism in children (Liew et al. 2015). Regarding ADHD, the prevalence in Asia
331 is below 5% according to the 15 pooled-study, which is not significantly different from the worldwide
332 prevalence of 5.29% (Polanczyk et al. 2007). It should be noted how each study define the case of
333 ADHD and ASD; e.g. medical record, diagnoses, questionnaires, etc. It is also important to keep
334 accumulating findings from not only the small but also the medium and large-sized cohorts, as well as
335 more detailed studies and studies with longer follow-up to provide evidence on child neurobehavioral
336 development in association with prenatal exposure to PFASs.
337
338 **4. Advantages and disadvantages of different-sized cohorts**
339 A recent study assessed the research outcomes of the European birth cohorts, and it indicated
340 that general cohort with 10,000-15,000 sample size allows for a broader contextual interpretation and
341 results in publishing a high number of articles, whereas cohorts of 3,000-10,000 sample size with a
342 specific focus receives a higher number of citations (Piler et al., 2017). However, Piler et al. (2017)
343 included only studies with sample size more than 3,000. As we have discussed in this manuscript,

many of the cohorts in Asia are smaller than sample size of 3,000. However even cohorts smaller than sample size of 3,000 were able to present significant findings as shown in the Table 2-6. Our experiences based on both the small Sapporo cohort (n = 514) and large scale Hokkaido cohort (n = 20,926), which was one of the models of the JECS, suggest that each cohort can provide significant and novel results. In Sapporo cohort, even low level *in utero* dioxin exposure may alter children's health status, such as birth weight, neurodevelopment, and immune function (Table 2). Moreover, findings of drastic inverse association between PFOS levels and essential fatty acids in maternal blood suggesting the importance of taking look at maternal metabolic resourses during pregnancy (Kishi et al., 2015). Recent publicaions suggested that PFOS and PFOA expoures *in utero* may alter reproductive and steroid hormone levels of infant at birth (Goudarzi et al., 2017b; Itoh et al., 2016). Not only PFASs but also phthalate and bisphenol A were found to have associations with children's reproductive and steroid hormones (Araki et al., 2014; Araki et al., 2016; Minatoya et al., *in press)*.

However, there are also limitations. The most relevant limitation of the small-scale cohort is the sample size and lack of statistical power. In addition, we should consider the effect size of findings from small cohort studies. Small cohort studies listed in the Tables 3-6 could only detect small to medium effect size (Cohen, 1988), even though these studies found statistical significance according to the p-values. Therefore, medium or large cohort studies are needed. Some of the findings from the PFASs investigations have been inconsistent. This could be due to the differences in dose-range and/or

362 composition of chemicals. Many of the environmental chemicals accompany various homologues and
363 congeners. Those chemicals might share similar exposure sources; therefore, a model with multiple
364 sources and differentiating their effects should be considered to avoid possible false-positive
365 conclusions (Kim et al., 2017). In addition, statistical errors should be taken into consideration. If there
366 is no true effect of PFAS on a certain outcome, then there might be type I error in some of the studies.
367 If the effect of PFASs on a certain outcome was true, then the direction of effect is supposed to be in
368 the same direction; in such a case, we should keep in mind that there might be type II errors in some
369 of the studies.

370 Compared to the small-sized Sapporo cohort, the strength of the Hokkaido cohort is that it
371 easier to detect relatively rare and/or low prevalence outcomes, such as stillbirth (0.32%, n=60),
372 preterm birth (4.9%, n=923), small for gestational age (7.0%, n=1,308), low birth weight (9.0%,
373 n=1,693), and birth defects (Hanaoka et al., 2017; Kishi et al., 2017). The prevalence of birth defects
374 in the Hokkaido cohort is shown in Table 7. The total number of all birth defects was 623 in 19,282
375 (3.7%) live births. The most frequent birth defect was circulatory system defect, under Classification
376 of International Statistical Classification of Diseases and Related Health Problems 10th Revision,
377 which occurred in 192 infants (0.99%). According to the calculation of sample size by the JECS study
378 protocol (JECS study protocol ver. 1.4), under conditions of significant level of 5%, statistical power
379 80%, and relative risk of 2.0, a sample size of more than 100,000 is necessary to test a hypothesis of

a disease/health outcome with a prevalence of 0.1% or less. An extremely large population-based cohort in Sweden included over 1.2 million participants with 20,074 (1.6%) cases of congenital heart defects (Persson et al., 2017). For even more rare diseases such as acute leukemia, an exposure affecting 5% of the population requires more than 1 million participants (Brown et al. 2007). In such a case, one birth cohort might not be sufficient to cover all participants, so an international project, such as The International Childhood Cancer Cohort Consortium, brings the various cohorts together (Brown et al. 2007).

The reduction in sample size, along with lack of follow-up, is another limitation of smaller cohorts. Although probability of loss-to-follow-up is a general disadvantage of a cohort study of any size, the impact of loss-to-follow-up could be greater for a small study than a large study, in terms of the possibility of lacking in occurrence of outcomes, e.g., ADHD and ASD. In addition, even longer follow-up periods are required when examining effects at the onset of puberty, and the number of participants might not be enough for analysis at that time point in a smaller cohort.

Moreover, potential biases may occur because of some study participants dropping out, which may cause under or over estimations. In addition, there might be confounding with other variables. We compared the basic characteristics of the participants in the Hokkaido cohort at baseline segregating those with and without available data at delivery, and the participants who were lost to follow up showed higher prevalence of nulliparity, drinking, smoking, and lower income during

pregnancy, and maternal lower education (Goudarzi et al. 2016a; Goudarzi et al., 2016b; Minatoya et al., 2017b). Having only biased participants with lower socioeconomic status who do not smoke may underestimate the potential risk of exposure. One of the reasons for inconsistent results between each cohort in the Asian countries as shown in Tables 3-6 may be because of small sample size. Larger sample size could provide statistical power and reliable results with smaller confidence intervals.

In a large cohort, such as a national cohort, the etiology and risk factors of rare diseases such as birth defects could be analyzed. On the other hand, large sample size studies also have difficulties. Among the most prominent is that large cohort studies include greater operating expenses, budgetary cost, and human resources. Magnus reported that Denmark (DNBC) and Norway (MoBa) have managed large population studies, partly because they have a unified public healthcare system and very good health registries (Magnus 2017). In Japan, there is no such registration system. Thus, each cohort has to send questionnaires to collect health data (Kawamoto et al., 2014; Kishi et al., 2017). Making use of the Hokkaido study and Tohoku cohort's 10-year experiences were keys to success in setting up JECS systematically. Similarly in Korea, experiences of several smaller cohorts are being applied to Ko-chens!

5. Future direction of Asian cohort

In conclusion-every cohort has importance; therefore, conducting studies in only one large scale cohort

in each country might not be always desirable. Even in a small cohort, a good design and original hypothesis brought novel findings. In a larger cohort, even more diverse findings will be expected by overcoming the limitation of small sample size. Nevertheless, International collaboration, such as the BiCCA, can overcome the inherent limitation of sample size. In addition to heterogeneity of exposure, ethnicity and socioeconomics, international comparison of nation-wide cohorts is warranted. As pointed out in BiCCA's first manuscript (Kishi et al., *in press*), potential limitations of the comparison of existing data among the studies are differences on basic demographic variables and questionnaires definition, environmental exposure measurements derived from various analytic methods or specimen, and heterogeneity of country or language-specific assessment tools. The potential bias could be verified by inter- and intra- laboratory tests; furthermore, evaluation of new methods and technologies would be enhanced by aggregating data from each cohort (Kishi et al., *in press*). Although there are many challenges to be overcome, future projects of meta-analysis, combining and harmonizing cohort data will enable researchers to improve statistical power and assess the exposure-outcome relationship, even for relatively rare health outcomes. Strengthening further collaborations not in only within Asia but also worldwide is essential to solve many global health issues.

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Table 1. Cohorts of Birth Cohort Consortium of Asia (BiCCA), alphabetical order of the country

	County	Name of cohort (abbreviation)	Study area	Recruitment period	N	Reference
1	Bangladesh	Harvard Reproductive and Birth Cohort (HRBC)	Pabna, Munshiganj	2008-2011	1613	(Kile et al. 2016)
2	China	Laizhou Wan Birth Cohort (LWBC)	South coast area of Laizhou Wan Handong province	2010-2013	773	(Gao et al. 2016)
3	China	Nanjing Medical University Birth Cohort (NJMUBC)	Nanjing, Suzhou, Wuxi, Huai'an, Changzhou	2014-2016	30,000 (targeted number)	-
4	China	Shanghai Birth Cohort (SBC)	Shanghai	2013-2018	3,000 (targeted number)	-
5	Japan	Hamamatsu Birth Cohort for Mothers and Children (HBC study)	Hamamatsu	2007-2011	1,138	(Takagai et al. 2016; Tsuchiya et al. 2010)
6	Japan	Hokkaido cohort: Hokkaido Study on Environment and Children's Health	Hokkaido	2003-2013	20,929	(Kishi et al. 2011; Kishi et al. 2013; Kishi et al. 2017)
7	Japan	Sapporo cohort: Hokkaido Study on Environment and Children's Health	Sapporo	2002-2005	514	(Kishi et al. 2011; Kishi et al. 2013; Kishi et al. 2017)
8	Japan	The Tohoku Study of Child Development (TSCD)	Sendai	2001-2006	1,323	(Nakai et al. 2004)
9	Korea	Children's Health and Environmental Chemicals in Korea (CHECK)	South Korea	2011-2013	352	(J. H. Kim et al. 2016)
10	Korea	COhort for Childhood Origin of Asthma and allergic diseases (COCOA)	Korea	2007-2028	1,734	(Yang et al. 2014)
11	Korea	Environment and Development of Children Study (EDC study)	Seoul	2008-2014	698	(Bae et al. 2017)
12	Korea	The Mothers and Children's Environmental Health study (MOCEH)	Seoul, Ulsan, and Cheonan	2006-2010	1,751	(B. M. Kim et al. 2009)
13	Korea	Panel Study on Korean Children (PSKC)	Korea	2008	2,150	(Jeong Rim Lee et al. 2017)
14	Malaysia	Universiti Sains Malaysia (USM) Pregnancy Cohort Study	Kubang Kerian	2010-2011	188	(Loy and Hamid Jan 2014)
15	Mongolia	Ulaanbaatar Gestation and Air Pollution Research (UGAAR)	Ulaanbaatar	2014-2015	540	-
16	Mongolia	Birth Cohort Study in Mongolia-Towards Solving Global Problems in the Maternal and Child Health	Borugan	2009-2010	Approx. 1000	(Takehara et al. 2016)
17	Nepal	Nepali Birth Cohort Study in Chitwan Valley	Chitwan	2008	100	(Parajuli et al. 2012)
18	Philippines	Cebu Longitudinal Health and Nutrition Survey (CLHNS)	Metro Cebu	1983-1984	3,327	(Adair et al. 2011)
19	Singapore	Growing Up in Singapore Towards healthy Outcomes (GUSTO)	Singapore	2009-2010	1,247	(Soh et al. 2014)
20	Sri Lanka	Kalutara Children's Health Study (KCHS)	Kalutara	2014-2015	315	-
21	Taiwan	Taiwan Birth Panel Study (TBPS)	Taipei, New Taipei	2004-2005	486	(Hsieh et al. 2011)
22	Taiwan	Taiwan Early-Life Cohort (TEC)	Hsinjuang, Jiayi, Yulin, Tainan, Kaohsiung, Taitung	2004-2005	1,589	(Wen et al. 2011)
23	Taiwan	Taiwan Maternal and Infant Cohort Study (TMICS)	Taipei, Hsinchu, Taichung, Changjua, Kaohsiung, Hualien	2000-2014	2577	(Y. Wang et al. 2014)
24	United Arab Emirates	Mother Infant Study Cohort (MISC)	Sharjah	2015-2016	259	-
25	Vietnam	BienHoa Dioxin Cohort study	Bien Hoa	2012	200	(Nishijo et al. 2012)
26	Vietnam	Dioxin and Development of Children in Vietnam	Hanoi, Phu, Cat, Bien Hoa	2008-2013	200	
27	Vietnam	DaNang Dioxin Cohort study	DaNang	2008-2010	241	-

Table 2. Prenatal dioxins exposure (TEQ pg/g lipid) and children's health, Sapporo cohort

Outcome	**N**	**Findings**	**Reference**
Birth weight	398	Significant decrease. Individual congener assessment found 2,3,4,7,8-PeCDF had a significant negative influence (per log 10 unit: β = -224.5 g; 95% CI: -387.4–-61.5).	(Konishi et al. 2009)
Thyroid hormones (TSH, free T4)	358	Log 10 Σdioxin (TEQ) was associated with increased infant free T4 (β = 0.224 ng/dL; 95% CI: 0.016-0.433) overall, and the association was more significant in boys (β = 0.299 ng/dL; 95% CI: 0.011-0.587).	(Baba et al. 2012)
IgE at birth	112	Total dioxin-like compounds were associated with decreased cord IgE in males (β = -1.01; 95% CI: -1.79, -0.23).	(Washino et al. 2007)
Neurodevelopment (BSID-II) 6 months	134	Several dioxin isomers showed adverse effects on motor development in 6-month-old male infants.	(Nakajima et al. 2006)
Neurodevelopment (BSID-II) 1.5 years	122	No association was observed between any of the dioxin isomers and neurodevelopment in males. In contrast, the levels of six dioxin isomers were significantly positively associated with mental development, and this unexpected finding might be attributable to residual confounding factors.	(Nakajima et al. *in press*)
Wheeze eczema Otitis media At 1.5 years	364	Polychlorinated dibenzofuran was associated with increased risk in male infants (OR: 2.5; 95% CI: 1.1–5.9). 2,3,4,7,8-PeCDF was associated with increased risk of otitis media (OR: 5.3; 95% CI: 1.5–19).	(Miyashita et al. 2011)
Intelligence (K-ABC) 3.5 years	144	K-ABC scores were not associated with prenatal exposure to dioxins.	(Ikeno et al. 2013)
Wheeze eczema Otitis media at 3.5 and 7 years	239	Total DLCs were associated with increased risk of wheeze in children up to aged 7 years (OR: 7.81; 95% CI: 1.4-43).	(Miyashita et al. 2017)

BSID-II, the Bayley Scales of Infant Development second edition; CI, confidence interval; DLCs, dioxin like compounds; K-ABC, Kaufman Assessment Battery for Children; OR, odds ratio; T4, thyroxine; PeCDF, penta-chlorinated dibenzofurans; TEQ, Toxicity equivalency quantity; TSH, thyroid stimulating hormone

Table 3. PFASs exposure on birth size, cord adipokines, and children's growth.

Name of the cohort, country	N	Exposure sample	Outcomes	Findings	Ref.
Sapporo cohort, Japan	428	2nd-3rd trimester Maternal blood	Birth weight and size	In utero exposure to relatively low levels of PFOS was negatively associated with birth weight.	(Washino et al. 2009)
	177	2nd-3rd trimester Maternal blood	Birth weight, Ponderal index, and IGF2 methylation	Increases in both PFOS and PFOA were associated with reduced ponderal index at birth. IGF2 methylation showed a significant negative association with increase in PFOA. Mediation analysis suggested that reduced IGF2 methylation explained around 21% of the observed association between PFOA exposure and reduced ponderal index.	(Kobayashi et al. 2016)
	168	2nd-3rd trimester Maternal blood	Ponderal index, adipokines	PFOS was positively associated with cord adiponectin, but negatively associated with ponderal index at birth.	(Minatoya et al. 2017a)
TBPS, Taiwan	429	Cord blood	Birth weight and size	PFOS levels were inversely associated with gestational age, birth weight, and head circumference. Odds ratio of preterm birth, low birth weight, and small for gestational age increased with PFOS exposure. PFOA, PFNA, and PFUnDA were not observed to have any significant impact on birth outcomes.	(Chen et al. 2012)
TMICS, Taiwan	223	3rd trimester Maternal blood	Birth weight and size; childhood weight and height at approximately 2, 5, 8, and 11 years of age	In girls, prenatal PFNA, PFDA, PFUnDA, and PFDoDA concentrations were inversely associated with birth weight. Prenatal PFDA and PFUnDA were associated with elevated odds of small for gestational age. PFDA, PFUnDA, and PFDoDA were associated with lower average childhood height z-score. In boys, prenatal PFNA and PFDoDA were associated with reduction in height at certain ages in childhood, but not with size at birth.	(Y. Wang et al. 2016)
Gyeongbuk county, Korea	59	Cord blood	birth weight, birth length and Ponderal index	Umbilical cord PFHxS concentration showed a significant inverse association with birth weight (OR = 0.26; 95% CI, 0.08-0.85) and a marginally significant inverse association with birth length (OR = 0.33; 95% CI, 0.09-1.17).	(Y. J. Lee et al. 2013)
Guangzhou Birth Cohort Study, China	321	Cord blood	Birth weight	Higher cord serum PFOS, PFOA, and isomers of PFOS were associated with lower birth weight. The association between cord PFAS level and birth weight was more pronounced in male infants. Branched PFOS isomers show greater impact on infant birth weight than linear PFOS.	(Li et al. 2017)
Haidian Maternal and Child Health Hospital, Beijing. China	170	Cord blood	Birth weight, birth length and ponderal index	The exposure levels of PFASs had no statistically significant associations with birth weight, birth length or Ponderal index. For male infants, PFHxS positively correlated with birth length, but the levels of PFUnDA were negatively associated with birth length.	(Shi et al. 2017)

CI; confidence interval, *IGF2*; *insulin-like growth factor 2*, OR, odds ratio; PFAS, Perfluoroalkyl substances; PFDoDA; perfluorododecanoic acid, PFHxS; perfluorohexane sulfonate, PFNA; perfluorononanoic acid, PFOA; perfluorooctanoate, PFOS; perfluorooctanesulfonic acid, PFUnDA; perfluoroundecanoic acid

Table 4. Perfluoroalkyl substances and thyroid hormones in mothers and infants

Name of the cohort, country	N	Exposure measures	Hormone samples	Findings	Ref.
TMICS, Taiwan	285	3rd trimester Maternal blood	3rd trimester Maternal blood Cord blood	Maternal PFHxS was positively associated with maternal TSH. Pregnant women with higher levels of PFNA, PFUnDA, and PFDoDA had lower free T4 and total T4. Maternal PFNA, PFUnDA, and PFDoDA were associated with lower cord total T3 and total T4, and PFDA with lower cord total T3.	(Y. Wang et al. 2014)
Sapporo cohort, Japan	392	2nd-3rd trimester Maternal blood	1st trimester Maternal blood Infant's heel-prick	Maternal PFOS levels were inversely correlated with maternal serum TSH and positively associated with infant serum TSH levels, whereas maternal PFOA showed no significant relationship with TSH or free T4 levels in mothers and infants.	(Kato et al. 2016)
Seoul, Korea	44	3rd trimester Maternal blood Cord blood	Cord blood	Maternal PFOS was inversely associated with fetal T3, and maternal PFTrDA was inversely associated fetal T4 and T3.	(S. Kim et al. 2011)
EBGRC, Korea	279	Cord blood	Cord blood	Cord blood PFPeA was positively associated with cord blood T4. In girls, PFPeA and PFHxS significantly increased T4 and T3, while PFNA decreased TSH.	(Shah-Kulkarni et al. 2016)
TBPS, Taiwan	118	Cord blood	Cord blood	PFOS in cord blood was positively associated with cord blood TSH, and inversely associated with cord blood T4. Those associations were more significant in boys.	(Tsai et al. 2017)

PFAS, Perfluoroalkyl substances; PFDoDA; perfluorododecanoic acid, PFHxS; perfluorohexane sulfonate, PFNA; perfluorononanoic acid, PFOA; perfluorooctanoate, PFOS; perfluorooctanesulfonic acid, PFPeA; perfluoropentanoic acid, PFTrDA; perfluorotridecanoic acid, PFUnDA; perfluoroundecanoic acid, T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone

Table 5. Allergic disease and immune function

Name of the cohort, country	N	Exposure measures	Outcome measures	Age	Findings	Ref.
TBPS, Taiwan	244	Cord serum	IgE	At birth, 2 years	Prenatal PFOA and PFOS exposure were positively correlated with cord blood IgE levels (when log increase of PFOA and PFOS, β = 0.134 and 0.161, respectively), but not associated with IgE at 2 years old.	(I. J. Wang et al. 2011)
			atopic dermatitis	0-2 years	No association with atopic dermatitis.	
Sapporo cohort, Japan	231	2nd -3rd trimester Maternal serum	IgE	at birth	Cord IgE levels decreased with high maternal PFOA concentration in females.	(Okada et al. 2012)
	343		Wheeze eczema	1.5 years	No associations between maternal PFOS and PFOA levels and food allergy, eczema, wheezing, or otitis media in 18-month-old infants.	
Hokkaido cohort, Japan	2,063	3rd trimester Maternal plasma	Wheeze, eczema and rhino-conjunctivitis	0-2 years	At 24 months, reduced risk of eczema with higher maternal PFTrDA levels was found	(Okada et al. 2014)
	1,558	3rd trimester Maternal plasma	Wheeze, eczema and rhino-conjunctivitis	4 years	Prenatal PFTrDA and PFDoDA showed negative association with risk of eczema and total allergic diseases.	(Goudarzi et al. 2016a)
	1,558	3rd trimester Maternal plasma	Common infectious diseases	0-4 years	PFHxS and PFOS were associated with higher risk of common infectious disease (Q1 vs. Q4 OR: 1.55; 95% CI: 0.976–2.45).	(Goudarzi et al. 2017a)

CI; confidence interval, OR; odds ratio, PFDoDA; perfluorododecanoic acid, PFHxS; perfluorohexane sulfonate, PFOA; perfluorooctanoate, PFOS; perfluorooctanesulfonic acid, PFTrDA; perfluorotridecanoic acid

Table 6. Perfluoroalkyl substances exposure on child neurodevelopment and behavioral problems

Name of the cohort, country	**N**	**Exposure measurements**	**outcomes**	**age**	**Findings**	**Ref.**
TBPS, Taiwan	239	Cord blood	Neurodevelopment using Comprehensive Developmental Inventory for Infants and Toddlers	2 years	Prenatal exposure to PFOS, but not PFOA, may affect children's development, especially gross-motor development at 2 years of age.	(Chen et al. 2013)
TMICS, Taiwan	120	3rd trimester maternal blood	full scale intelligence quotient (FSIQ), verbal IQ (VIQ) and performance IQ (PIQ)	5 and 8 years	Prenatal PFUnDA concentrations were inversely associated with children's performance IQs at age 5 years. Children with higher prenatal PFNA levels had lower verbal IQ at age 8 years.	(Y. Wang et al. 2015)
Hokkaido cohort, Japan	173	3rd trimester maternal blood	Neurodevelopment using Bayley Scales of Infant Development (BSID II)	6 and 18 months	PFOA was negatively associated with mental development in girls at 6 months but not at 18 months.	(Goudarzi et al. 2016b)
TBPS & TEC, Taiwan	282	Cord blood	ADHD related neurobehavioral symptoms	7 years	Prenatal exposure to PFNA (but not PFOA, PFOS, or PFUnDA) was found to be associated with neurobehavioral symptoms related to ADHD in 7-year-old children.	(Lien et al. 2016)

ADHD; Attention Deficit Hypertension Disorder, PFOA; perfluorooctanoate, PFNA; perfluorononanoic acid, PFOS; perfluorooctanesulfonic acid, PFUnDA; perfluoroundecanoic acid

Table 7. Prevalence of birth defects observed in the Hokkaido Study

Categories of birth defect	Number N=19282	percent (%)
Any birth defect	623	3.23
ICD 10th Codes		
Nervous system (Q00-07)	21	0.11
Eye, ear, face, and neck (Q10-18)	39	0.20
Circulatory system (Q20-28)	192	0.10
Respiratory system (Q30-34)	4	0.02
Cleft lip and cleft palate (Q35-37)	41	0.21
Digestive system (Q38-45)	31	0.16
Genital organs (Q50-56)	89	0.46
Urinary system (Q60-64)	50	0.25
Musculoskeletal system (Q65-79)	91	0.47
Skin, unspecified (Q80-89)	32	0.17
Other congenital malformations (Q80-89)）	19	0.10
Chromosomal abnormalities, not elsewhere classified (Q90-99)	42	0.22
Total	651 (28 cases overlap)	3.38

Including data at birth and 1, 2, 4, and 7 years follow-up

Figure legends

Figure 1 Concentrations of dioxin in human milk between 1999-2005（TEQ pg/g lipid)
The bars show mean or median levels of PCDDs + PCDFs (+ Dioxin-like-PCB) (toxic equivalents (TEQ) pg/g lipid) in breast milk. The followings are country, sampling period, and reference.

Netherlands: 2001–2003 (Nakatani et al. 2005), Italy: 2001–2003 (Nakatani et al. 2005), Germany: 2001–2003 (Nakatani et al. 2005), the United States: 2001–2003 (Nakatani et al. 2005), Japan: Sapporo: 2002-2005 (Todala et al. 2010), Japan: Tohoku: 2001-2003 (Nakamura et al. 2008), Japan: Oosaka: 1999 (Nakatani et al. 2005), China: 2002 (Nakatani et al. 2005), Korea: 2002 (Nakatani et al. 2005), Taiwan: 2000-2001 (Nakatani et al. 2005).

Figure 2 Maternal/Cord blood levels of PFOS and PFOA in different studies (ng/mL)

The bars show either maternal or cord blood levels of PFOS (ng/ml) and PFOA (ng/ml). (m) stands for maternal blood, and (c) stands for cord blood, respectively.Values are mean, median or geometric mean. The followings are Country, Name of the study, sampling period, and reference.

Canada: MIREC, 2008-2011 (Ashley-Martin et al. 2017). USA: Project VIVA, 1999-2002 (Fleisch et al. 2017). Denmark: Odense Child Cohort, 2010-2012 (Dalsager et al. 2016). Norway: MoBa, 2003-2004 (Granum et al. 2013); MISA study, 2007-2009 (Berg et al. 2017). Netherland: LINK, 2011-2013 (de Cock et al. 2014).Japan: Hokkaido, 2003-2011 (Kishi et al. 2017); Sapporo, 2002-2005 (Okada et al., 2012). China: Beijing, 2012 (Shi et al. 2017); Gaungzhou Birth cohort, 2013 (Li et al. 2017). Korea: Gyeongbuk, 2011 (Lee et al. 2013); EBGRC, 2006-2012 (Shah-Kulkarn et al. 2016); Seoul, 2008-2009 (Kim et al. 2011).Taiwan: TMICS, 2000-2001 (Wang et al. 2016); TBPS, 2004-2005 (Chen et al. 2012).

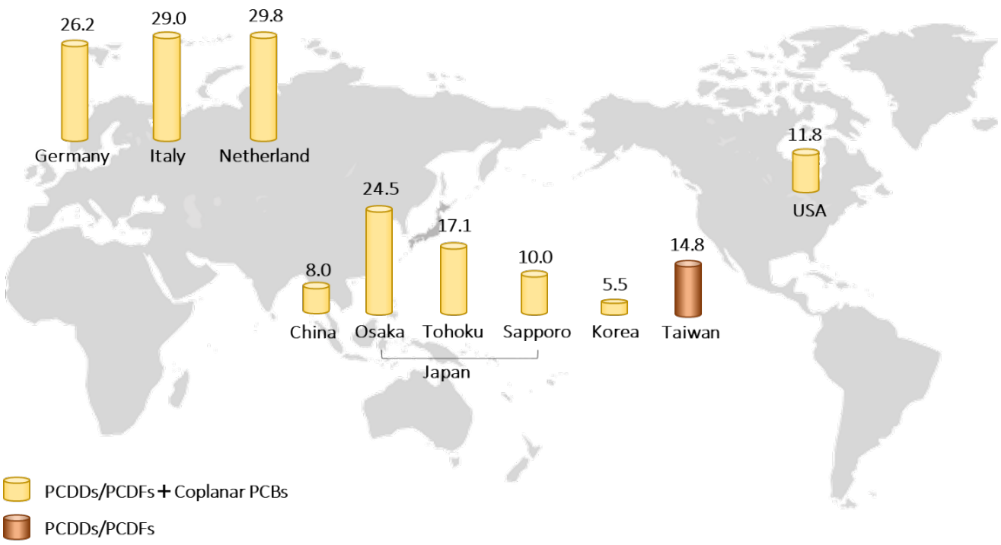

Fig 1. Concentrations of dioxin in human milk between 2001-2005 (TEQ pg/g lipid)

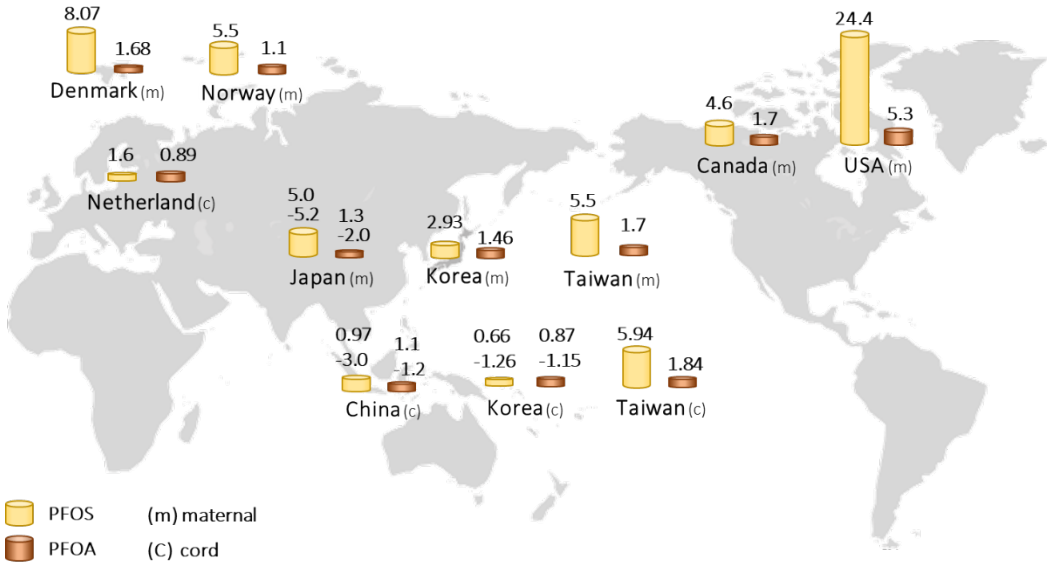

Fig 2. Maternal/Cord blood levels of PFOS and PFOA in different studies (ng/mL)