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Introduction of the Hokkaido study and impact of PFAS on childhood asthma and allergies and infectious diseases

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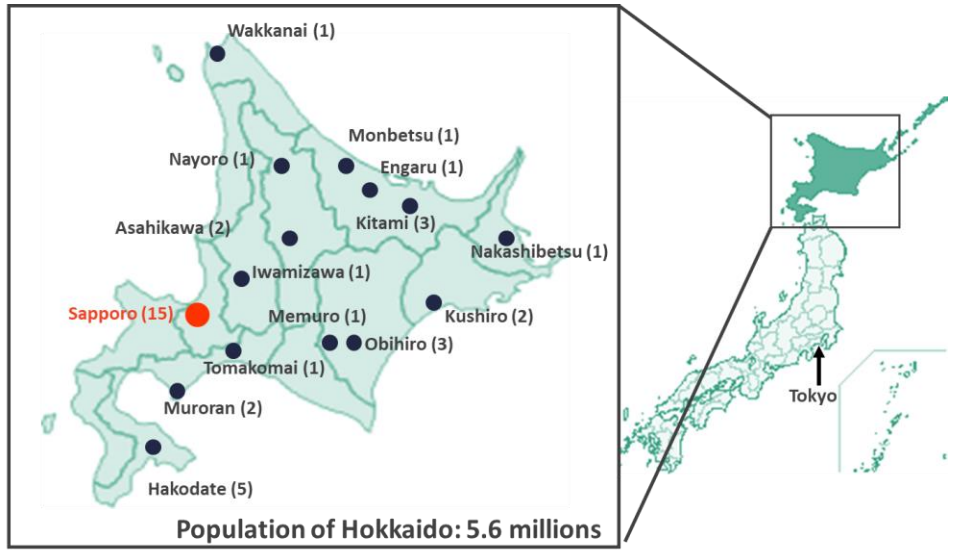
Outline

1. Brief introduction of the Hokkaido Study
2. Findings from the Hokkaido Study
   - Impact of PFAS on childhood asthma and allergies and infectious diseases

Birth Cohorts: the Hokkaido Study of Environment and Children's Health

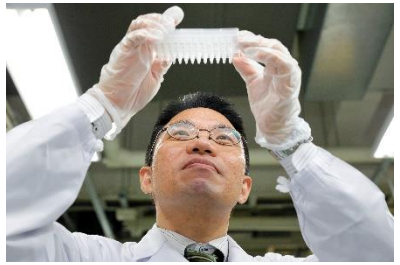


Cohort	Recruitment periods	number recruited
Sapporo	2002-2005	**514** (1 hospital)
Hokkaido	2003-2012	**20,926** (37 hospitals)

Objectives

1. To find the effects of perinatal environmental factors on birth outcomes including congenital anomalies and children's growth.
2. To evaluate the prevalence of allergic diseases, developmental and neurobehavioral disorders.
3. To identify a high-risk group classified by genetic susceptibility (SNPs) and investigate trans-generational epigenetic effects of environmental chemicals.
4. To provide scientific evidence for health policies based on epidemiological data.

Follow-up survey and sample collection

	At pregnancy		At birth	Infancy to Childhood							
Questionnaire based survey	**IC & Baseline Q** Parental basic information		**Birth Record** Birth outcomes & congenital abnormality	**Q for 4M** Physical Growth Allergy ISAAC Smoking	**Q for 1Y** Physical Growth Allergy ISAAC Smoking	**Q for 1.5Y** SES, M-CHAT	**Q for 2Y** Physical Growth Allergy ISAAC Smoking	**Q for 3Y** SES, KIDS	**Q for 4Y** Physical Growth Allergy ISAAC Smoking	**Q for 5Y** SDQ, DCDQ, SES	**Q for 6Y** SCQ, ADHS-RS, Home
	<13w	3rd	At Birth	4 M	1 Y	1.5 Y	2 Y	3 Y	4 Y	5 Y	6 Y
Sample collection	**Maternal Blood**	**Maternal Blood**	**Maternal blood & hair, Cord blood**	**These samples were used for Maternal & Child's biomonitoring, Chemical Exposure Measurement Genetic Factors (SNPs), Child's Epigenetics**							
Face to Face survey										**Anthropometry for 5 to 13Y**	

Cont.

Schooler & Puberty | **Adult**

Questionnaire for cellphone & 5G use in 2020 to 2024 for all participants

Questionnaire based survey

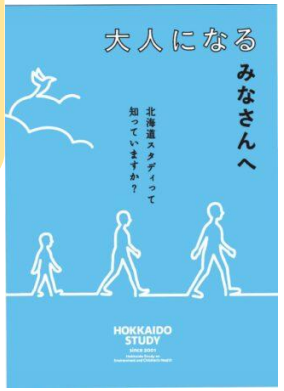
7 Y	8 Y	9-11 Y	14-17 Y	18 Y
Q for 7Y Allergy ISAAC Smoking (Home environment)	**Q for 8Y** ADHD (Conners3P, ADHD-RS), PSAI-J, EES, Life event, ASQ, CBCL, PSI	**Q for 9-12Y** Onset of Puberty Height, weight	**Q for 13-15Y** Onset of Puberty Height, weight	**Q for 17Y** Allergy ISAAC Smoking (Home environment)
				IC & Q for 18Y Height, weight, Lifestyle & Social adaptability

Sample collection

- **Child's Urine & House Dust** (7 Y)
- **Child's Urine & Blood** (9-11 Y)
- **Child's Urine, Blood & House Dust** (14-17 Y)

Face to Face survey

- **Home Visit** at 7Y
- **WISC-IV** at 8Y
- **Medical Interview** for 9 to 11Y
- **Medical Interview** for 14 to 17Y
- **ERP** for 9 to 16Y
- **Anthropometry** for 5 to 13Y
- **WISC-IV** for 15 to 16Y



HOKKAIDO STUDY
since 2001
Hokkaido Study on Environment and Children's Health

Target environmental chemicals

Persistent Organic Pollutants (POPs)

- **Dioxins and PCBs (66 congeners)**
- **Organochlorine pesticides (OCP)**
- **Per- and polyfluoroalkyl substances (PFAS)**

Pesticides

Fluorinated products

Water resistant products

PCBs

Food

Food packages

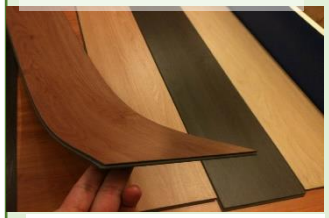
Short half-lives

- **Phthalates and alternative plasticizers**
- **Bisphenols (BP)**
- **Phosphate flame retardants (PFR)**
- **Nonyl phenols (NP)**

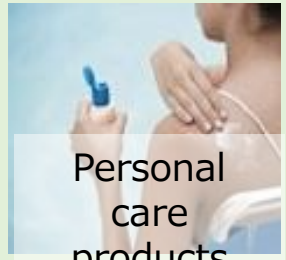
cans

Polycarbonate goods

floor materials



electronics



Personal care products

Food containers

floor wax

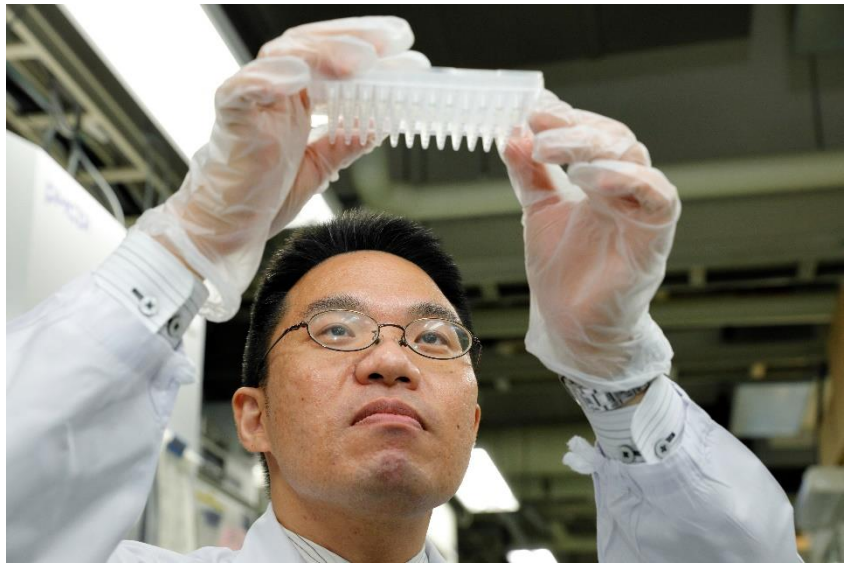
toys

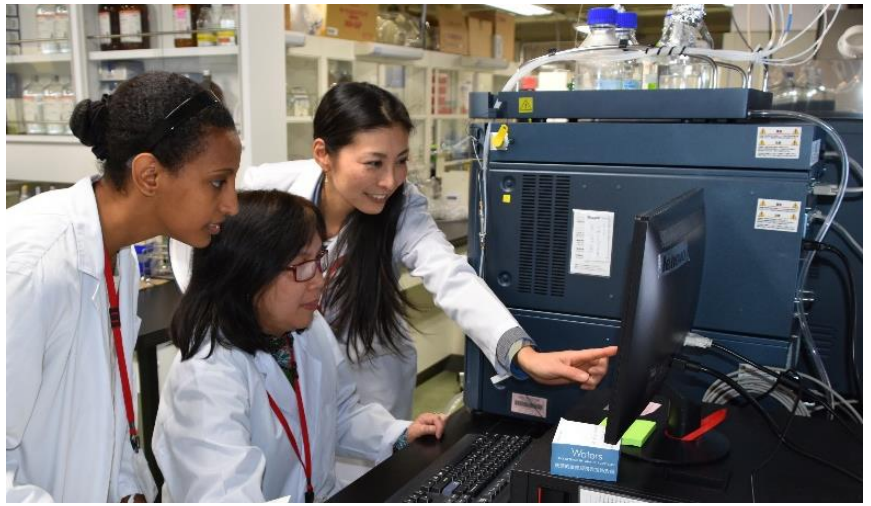
Flammable textile

Biological measurements

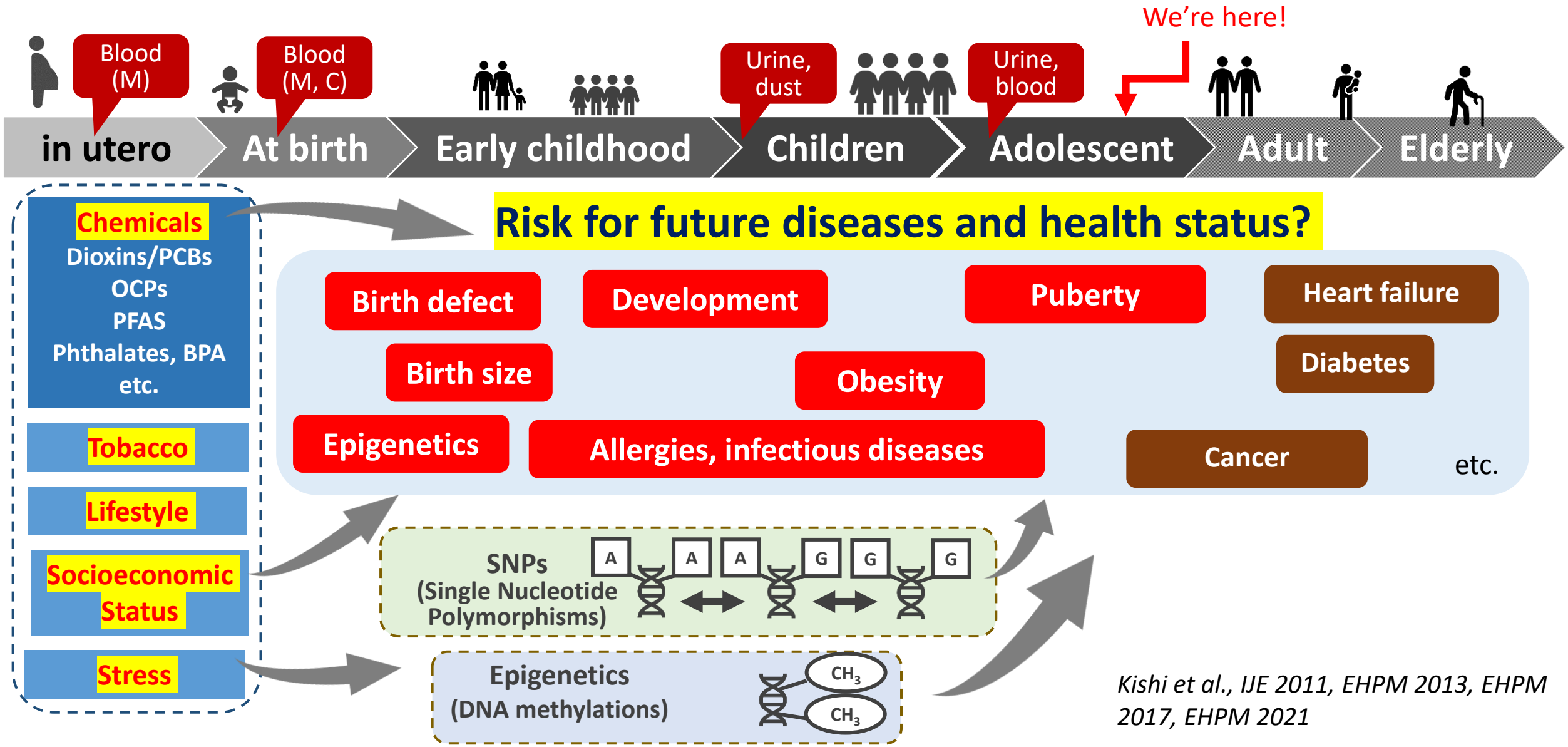
Variables	Specimen
Cotinine*	Maternal blood
Folic acid*	Maternal blood
Fatty Acids and triglyceride**	Maternal blood
IgE, IgA**	Cord blood
Thyroid hormones: TSH, fT4 fT3*	Maternal and cord blood
Reproductive hormones: steroid hormones, prolactin, LH, FSH, SHBG, Inhibin B, INSL3	Cord blood
Genes (SNPs, DNA methylation)	Maternal and cord blood

*Hokkaido Only, **Sapporo Only





Long Follow-up of the participants



Kishi et al., IJE 2011, EHPM 2013, EHPM 2017, EHPM 2021

Various outcomes and their risk factors

Outcomes		Associated risk factors （Journal name, year）
Birth outcomes and Growth		Tobacco smoke (Cotinine) （BMJ Oepn, 2019）, Caffeine （Pediatric Res, 2017）, Folic Acid （Brit J Nutrit ; JE2019）, Educational level, BMI （IJERPH, 2018; Matern. Child Health J, 2021), Risk score （Clin Pediat Endocrinol, 2019）、Steroid Hormones （Am J Human Biol、2018） Dioxins （Environ Res, 2009), Perfluoroalkyl substances （EHP, 2009; JESEE, 2017, Env Int 2020), Me-Hg （STOTEN, 2015）, Phthalates （STOTEN, 2017）、Pregnancy Hypertensive Disorder （IJERPH, 2021）、
Thyroid hormones		Perfluoroalkyl substances （EHPM, 2016; Environ Int, 2019）, Dioxins （STOTEN, 2018）、OH-PCB （Environ Res 2018）, Organochlorine pesticides (Env Res 2020)
Reproductive hormones, adipokines Sexual dimorphism		Perfluoroalkyl substances （Environ Int, 2016; EHP, 2017; Environ Res, 2017）, Phthalates （PLOS One, 2014; STOTEN, 2017）, Bisphenol A （Epidemiology, 2017）, Organochlorine pesticides （Environ Int, 2018）, Dioxins （Environ Int, 2018）、Reproductive Hormones （PLOS One 2015; Pediatr Int, 2019）
Neurodevelopment		Socioeconomic factors （IEA, 2014; Child Care Health Dev, 2017, Pediatr Int 2020）, Dioxins （EHP, 2006; Environ Res, 2017; STOTEN, 2018）, Organochlorine Pesticides (Neurotoxicology, 2018), Perfluoroalkyl substances （STOTEN, 2016）, Bisphenol A （STOTEN, 2018）, Adipokines （IJERPH, 2018）
Asthma and allergies, infectious diseases		Dioxins （Environ Res, 2011; STOTEN, 2018）、Perfluoroalkyl substances （Environ Res, 2012; Environ Int, 2014, 2016, 2017, 2021）、Phthalates （STOTEN, 2018）、Phosphate Flame Retardants (Environ Int, 2019)
Gene-Environment Interaction		Tobacco smoke （Mol Human Reprod, 2006; Am J Epidemiol, 2008; J Epidemiol, 2012; Toxicol Lett, 2013; Reproduc Toxicol, 2016; STOTEN, 2017）、Sexual dimorphism （Steroid, 2019）, phthalate and bisphenol A (Steroid 2020)
Epigenetics		Tobacco smoke （Sci Rep, 2018）, Tobacco smoke and ADHD (Clin Epigenetics, 2021), Folate and allergies (Ped allerg Immunol, 2021), Perfluoroalkyl substances (IJHEE, 2018; Environ Int, 2018), Bisphenol A (Sci Rep, 2019)、Phthalate (STOTEN, 2021)
Exposure levels and trend		Perfluoroalkyl substances (EI 2014), Phthalates (IJHPH, 2021), Bisphenol A (Env Res 2020), Phosphate Flame retardants (IJHEH 2020)
Indoor	Asthma and allergies	Dampness, fuel use, ventilation （IAOEH 2013; JE, 2014）、Phthalates （STOTEN 2014; Environ Int 2016 ）、Phosphate Flame Retardants （Indoor Air, 2014; Environ Int, 2018; Environ Res 2019）、Microbial VOCs （STOTEN 2012)
	Sick Building Syndrome	Formaldehyde and VOCs (IAOEH 2009;2010; STOTEN 2012), Microbial VOCs （STOTEN、2010）、Phthalates and Phosphate Esters （Indoor Air 2010）、Fungi and dust mite allergen （Indoor Air, 2012）、Lifestyle (EHPM2020)

Outline

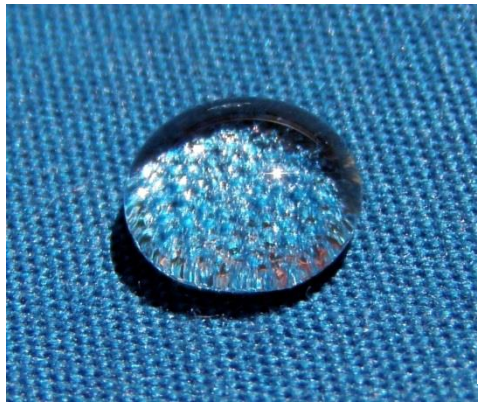
1. Brief introduction of the Hokkaido Study

2. **Findings from the Hokkaido Study**

   - **Impact of PFAS on childhood asthma and allergies and infectious diseases**

Per- and polyfluorinated substances (PFAS)

- PFAS are an organofluorine compounds with all hydrogens replaced by fluorine on a carbon chain.
- They have unique properties to make materials stain, oil, and water resistant, and their industrial applications are including water-proofing, insulating agents, and in fire extinguishing foam, etc.
- Main exposure sources are drinking water, food, food packaging, house dust *(Hölzer et al. 2008; Halldorsson et al. 2008; Begley et al. 2005; Björklund et al. 2009)*
- Biological half-life in humans are PFOS 5.4 years, PFOA 3.8 years *(Olsen et al. 2007)*

PFOS and PFOA in maternal/cord blood

PFOS/PFOA

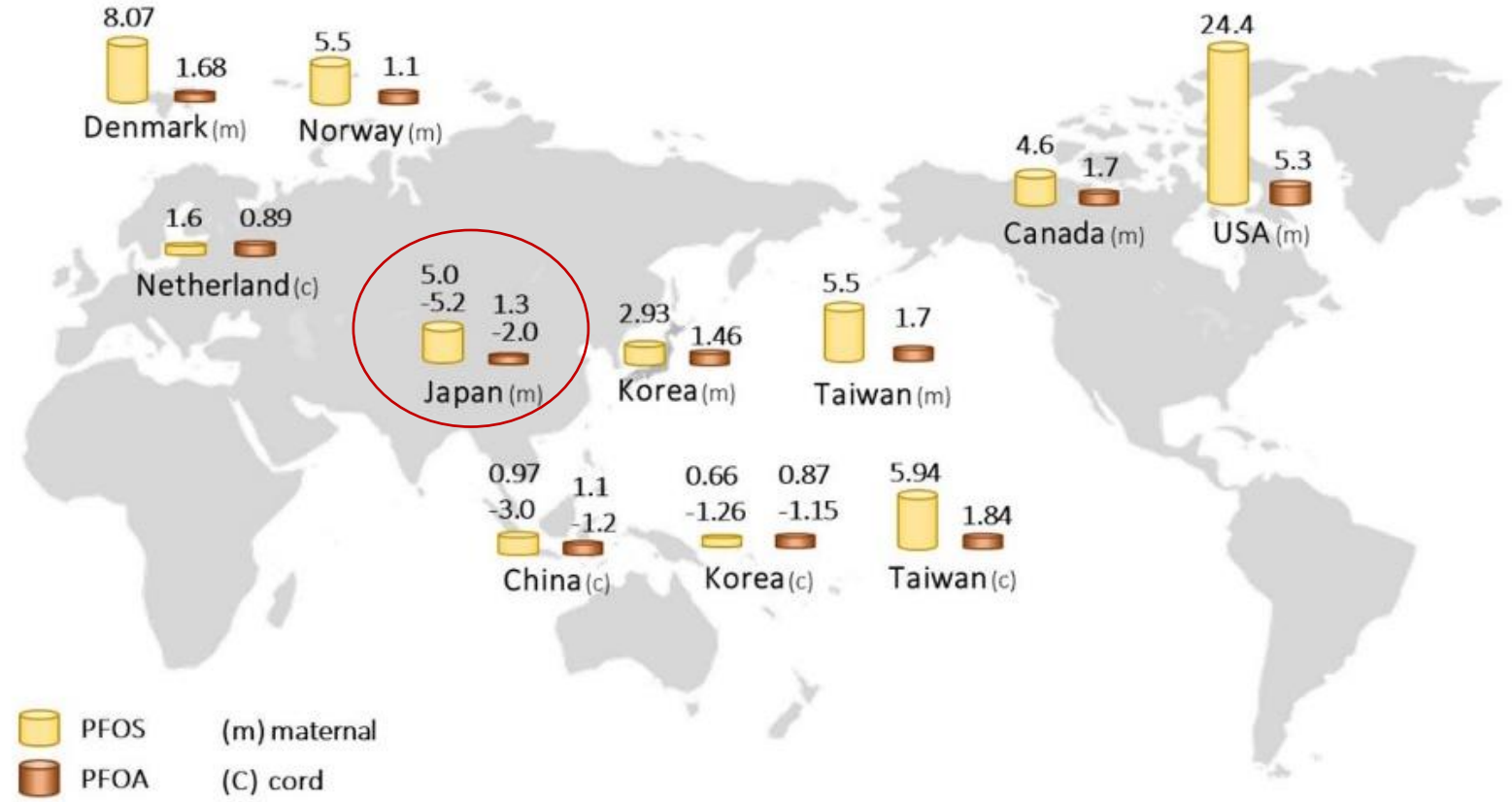
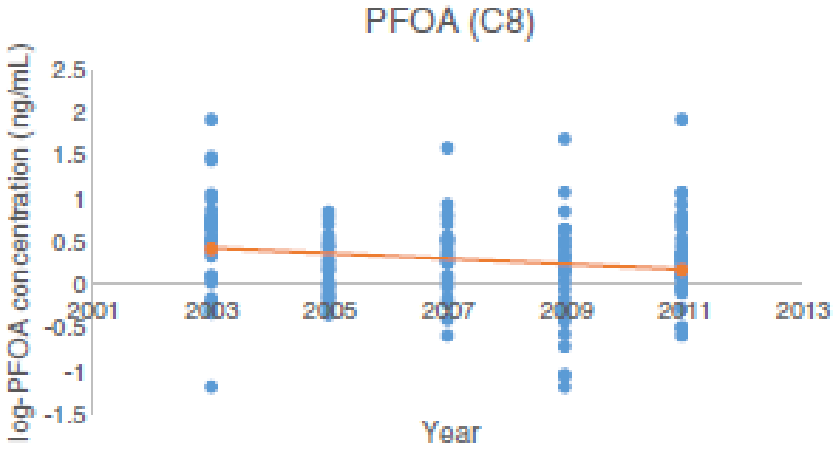
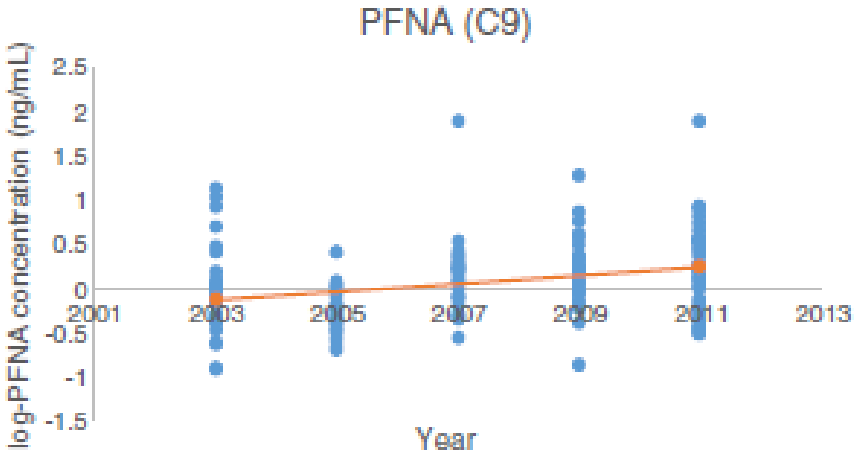


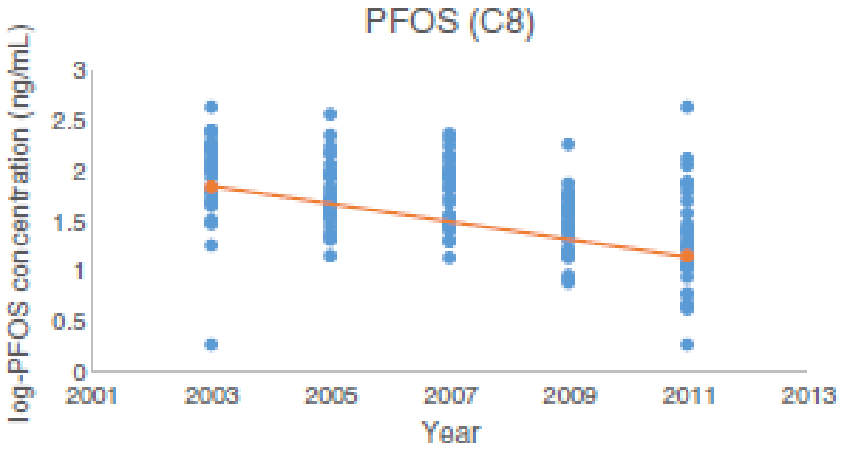
Fig. 2. Maternal/Cord blood levels of PFOS and PFOA in different studies (ng/mL). The bars show either maternal or cord blood levels of PFOS (ng/ml) and PFOA (ng/ml). (m) stands for maternal blood, and (c) stands for cord blood, respectively. Values are mean, median or geometric mean. The followings 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-Kulkarni 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).

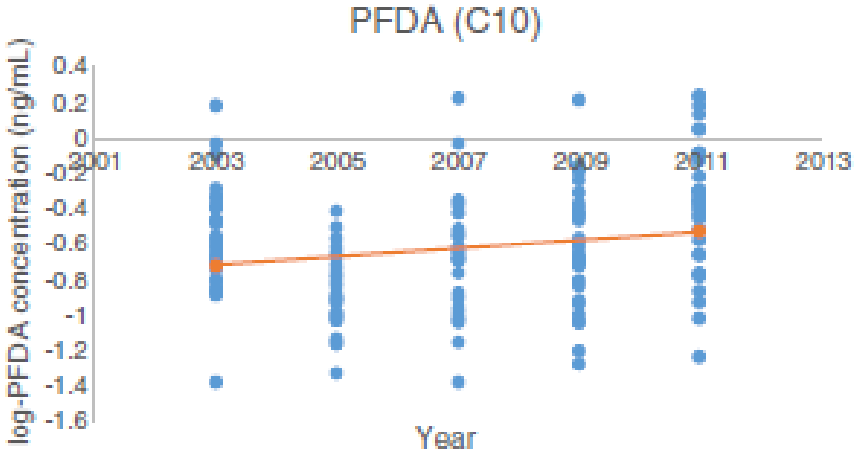
Kishi et al., STOTEN2017

Year trends of maternal PFAS 2003 - 2011



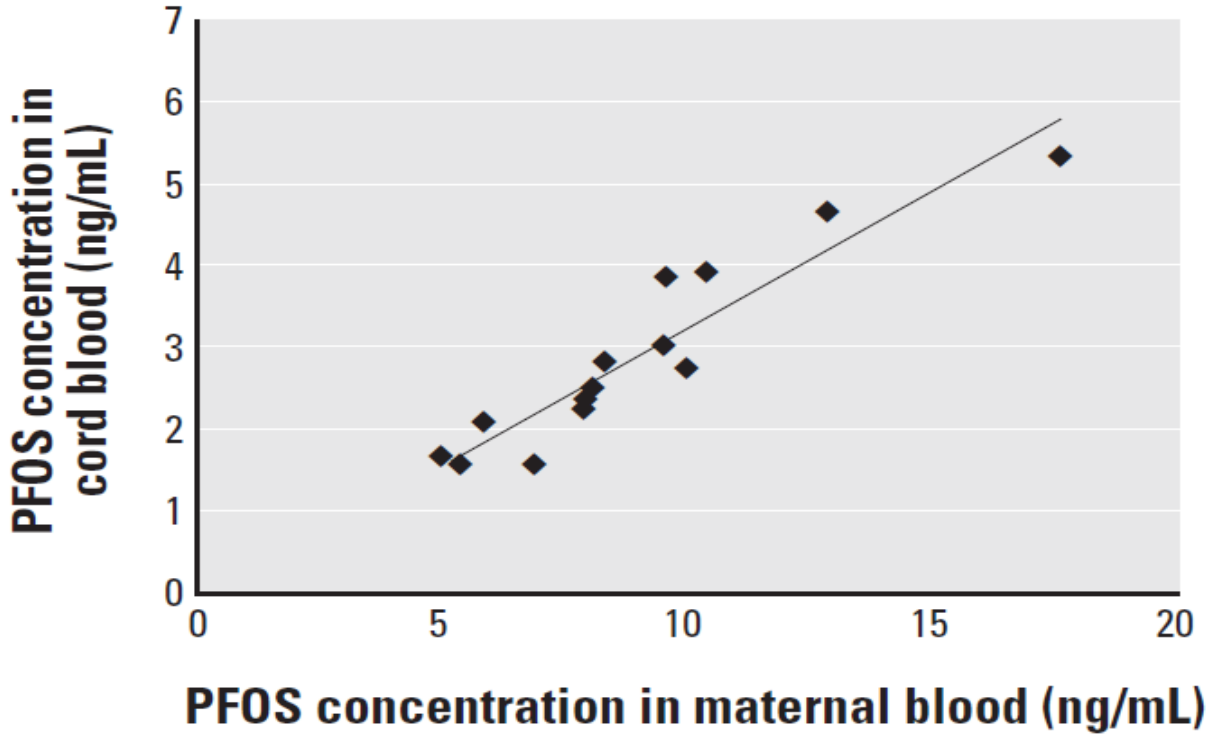






- **PFOS and PFOA concentrations declined**
- **PFNA and PFDA levels increased between 2003-2011**

Maternal to child transfer of PFOS



- Maternal PFOS level was positively correlated with cord blood PFOS level
- Suggesting that trans-placental transport

Inoue et al. EHP, 2004

Environmental Research 112 (2012) 118–125

Contents lists available at SciVerse ScienceDirect

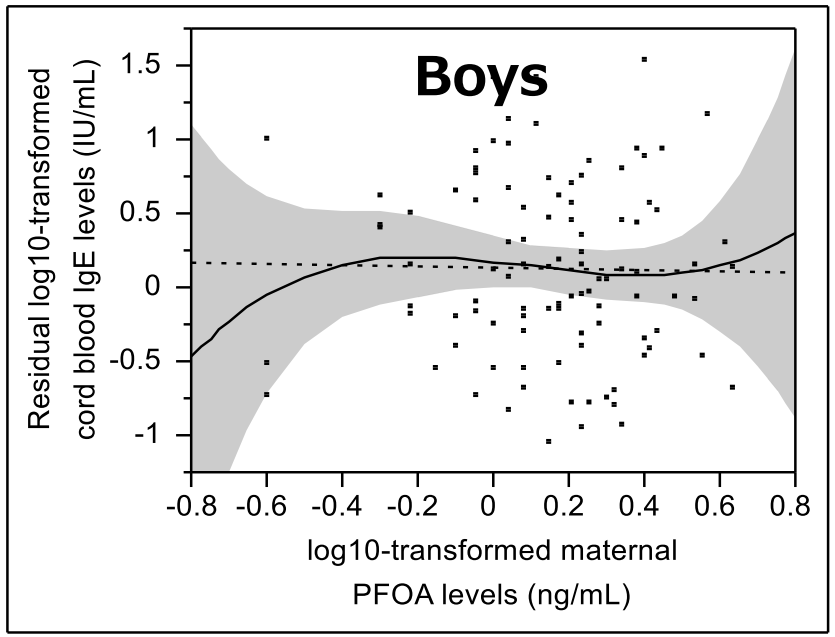
Environmental Research

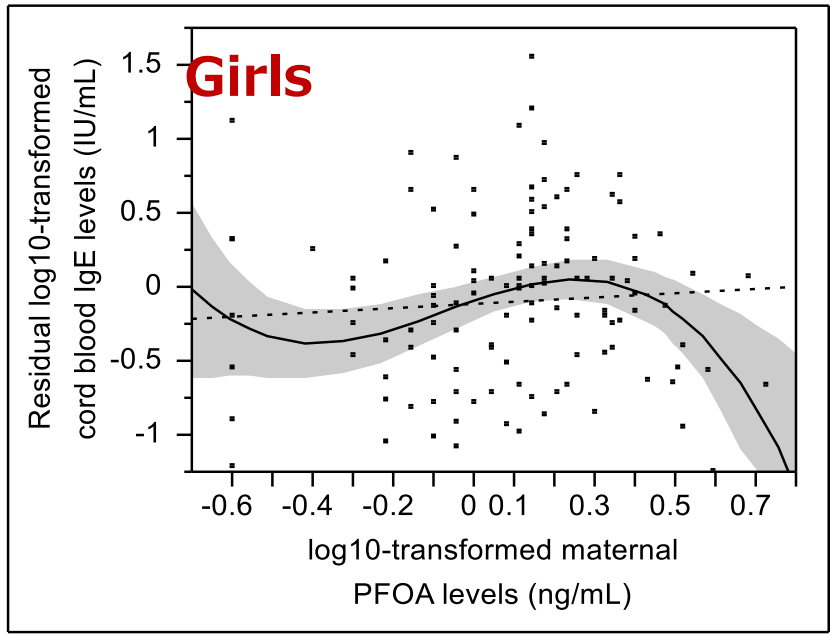
journal homepage: www.elsevier.com/locate/envres

Maternal PFOA and cord blood IgE

Prenatal exposure to perfluorinated chemicals and relationship with allergies and infectious diseases in infants☆

Emiko Okada[a], Seiko Sasaki[a], Yasuaki Saijo[b], Noriaki Washino[a], Chihiro Miyashita[a], Sumitaka Kobayashi[a], Kanae Konishi[a], Yoichi M. Ito[c], Rie Ito[d], Ayako Nakata[d], Yusuke Iwasaki[d], Koichi Saito[d], Hiroyuki Nakazawa[d], Reiko Kishi[e,*]





- **Cord blood IgE levels decreased significantly with high maternal PFOA concentration among female infants**
- **Our result was in line with C8 Health Project (US), which are exposed to higher level of PFOA**

Prenatal PFAS on allergies and infectious diseases at age 4

Environment International 94 (2016) 124–132

Contents lists available at ScienceDirect

Environment International

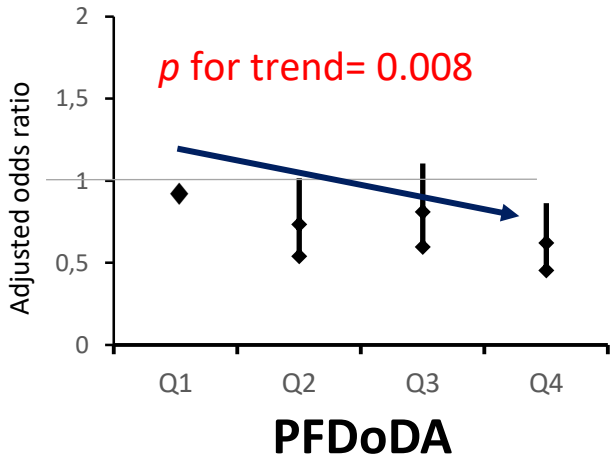
journal homepage: www.elsevier.com/locate/envint

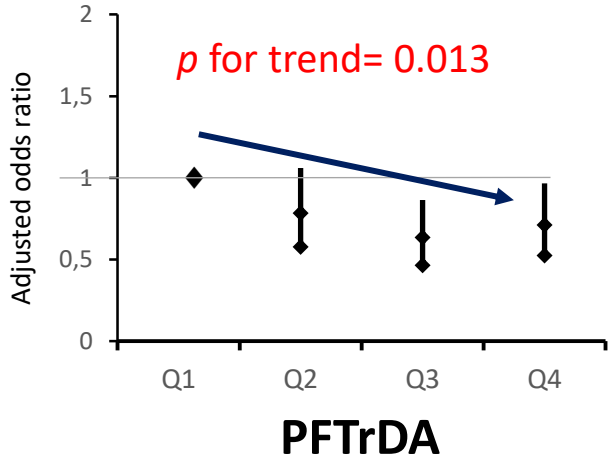
Full length article

Effects of prenatal exposure to perfluoroalkyl acids on prevalence ofallergic diseases among 4-year-old children

Houman Goudarzi [a], Chihiro Miyashita [a], Emiko Okada [b], Ikuko Kashino [a,c], Sumitaka Kobayashi [a], Chi-Jen Chen [a,d], Sachiko Ito [a], Atsuko Araki [a], Hideyuki Matsuura [a], Yoichi M. Ito [e], Reiko Kishi [a,*]

Allergy





Environment International 104 (2017) 132–138

Contents lists available at ScienceDirect

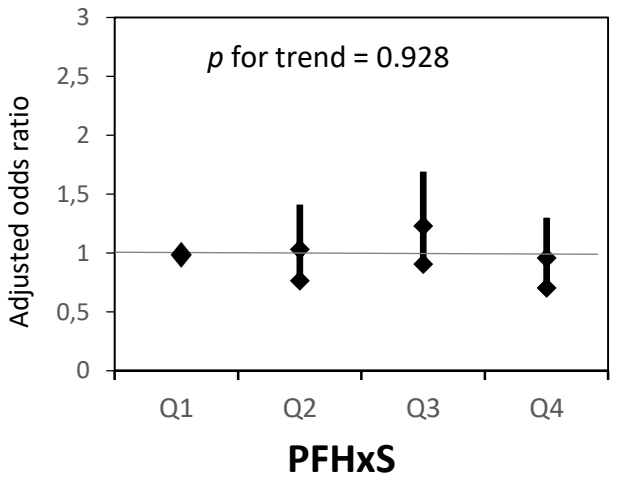
Environment International

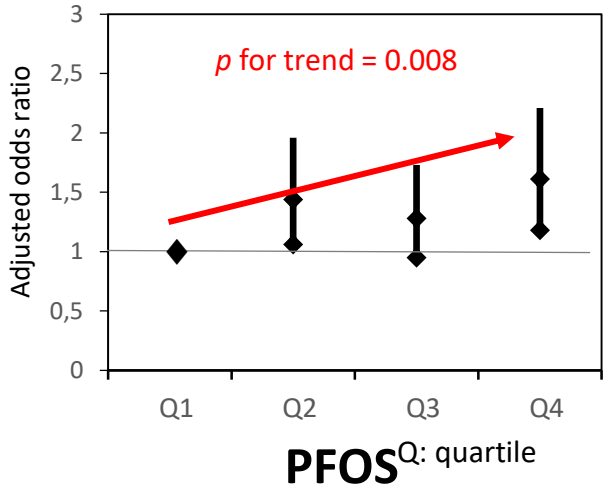
journal homepage: www.elsevier.com/locate/envint

Prenatal exposure to perfluoroalkyl acids and prevalence of infectious diseases up to 4 years of age

Houman Goudarzi [a], Chihiro Miyashita [a], Emiko Okada [b], Ikuko Kashino [a,c], Chi-Jen Chen [a,d], Sachiko Ito [a], Atsuko Araki [a], Sumitaka Kobayashi [a], Hideyuki Matsuura [a], Reiko Kishi [a,*]

Infectious diseases





Q: quartile

Adjusted ORs in the highest quartile vs lowest quartile for total allergic diseases were significantly decreased for PFDoDA (C12) and PFTrDA (C13). Associations were prominent among boys. Q: quartile. Logistic models were adjusted for maternal age, maternal educational level, parental allergic history, parity, children gender, day care attendance and ETS exposure in at 4-year-old, and breast feeding.

Environment International 143 (2020) 105979

Contents lists available at ScienceDirect

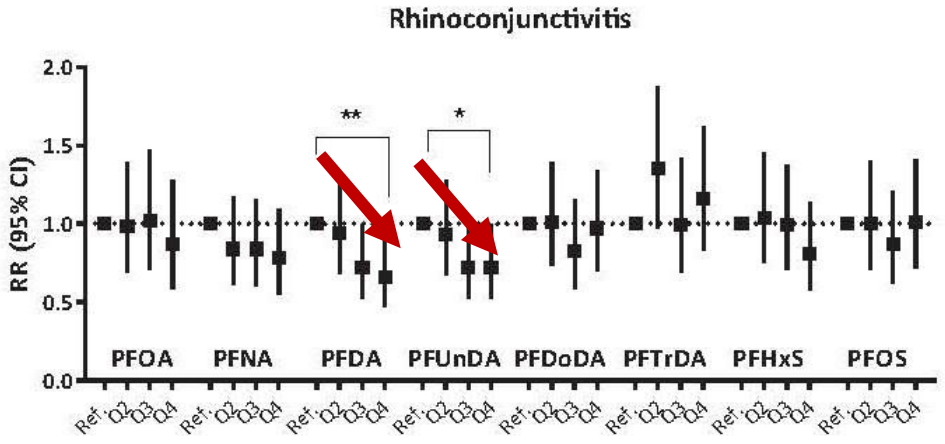
Environment International

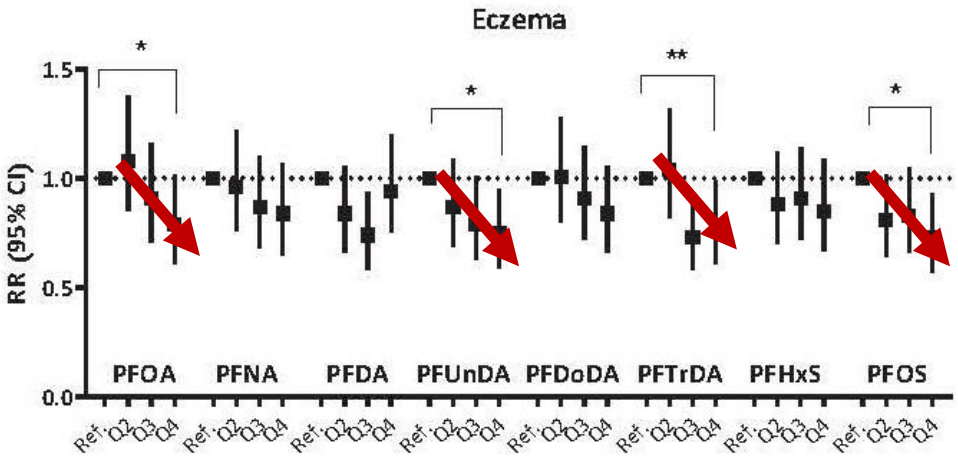
journal homepage: www.elsevier.com/locate/envint

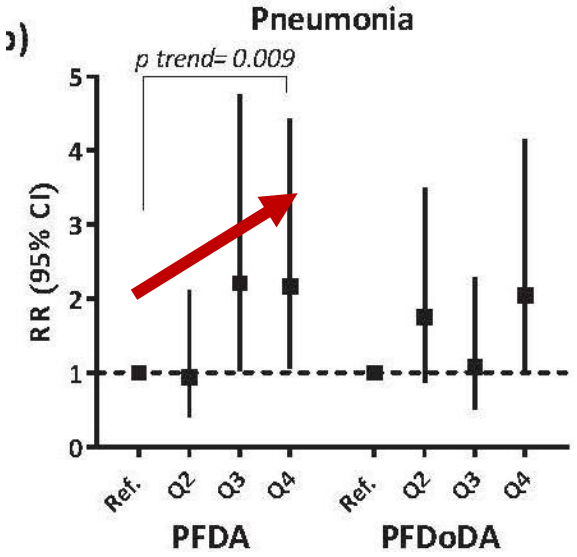
Prenatal PFAS on allergies and infectious diseases at age 7

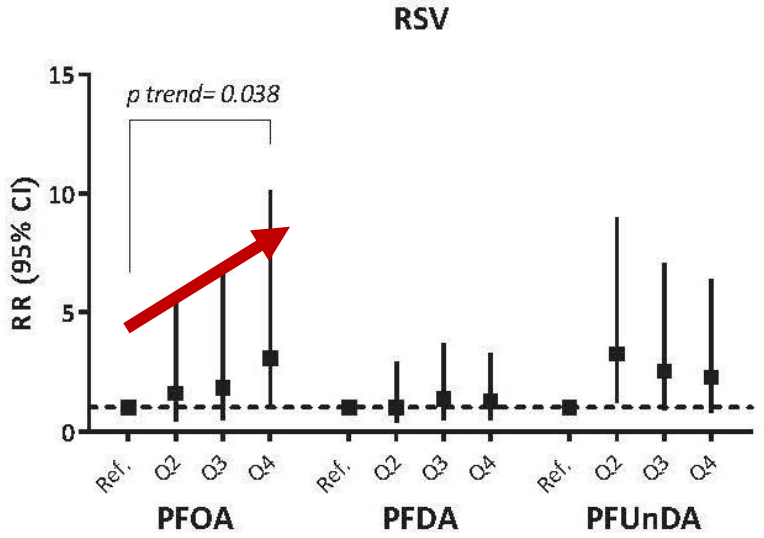
Effect of prenatal exposure to per- and polyfluoroalkyl substances on childhood allergies and common infectious diseases in children up to age 7 years: The Hokkaido study on environment and children's health

Yu Ait Bamai[a], Houman Goudarzi[a,b], Atsuko Araki[a], Emiko Okada[a,c], Ikuko Kashino[a], Chihiro Miyashita[a], Reiko Kishi[a,*]



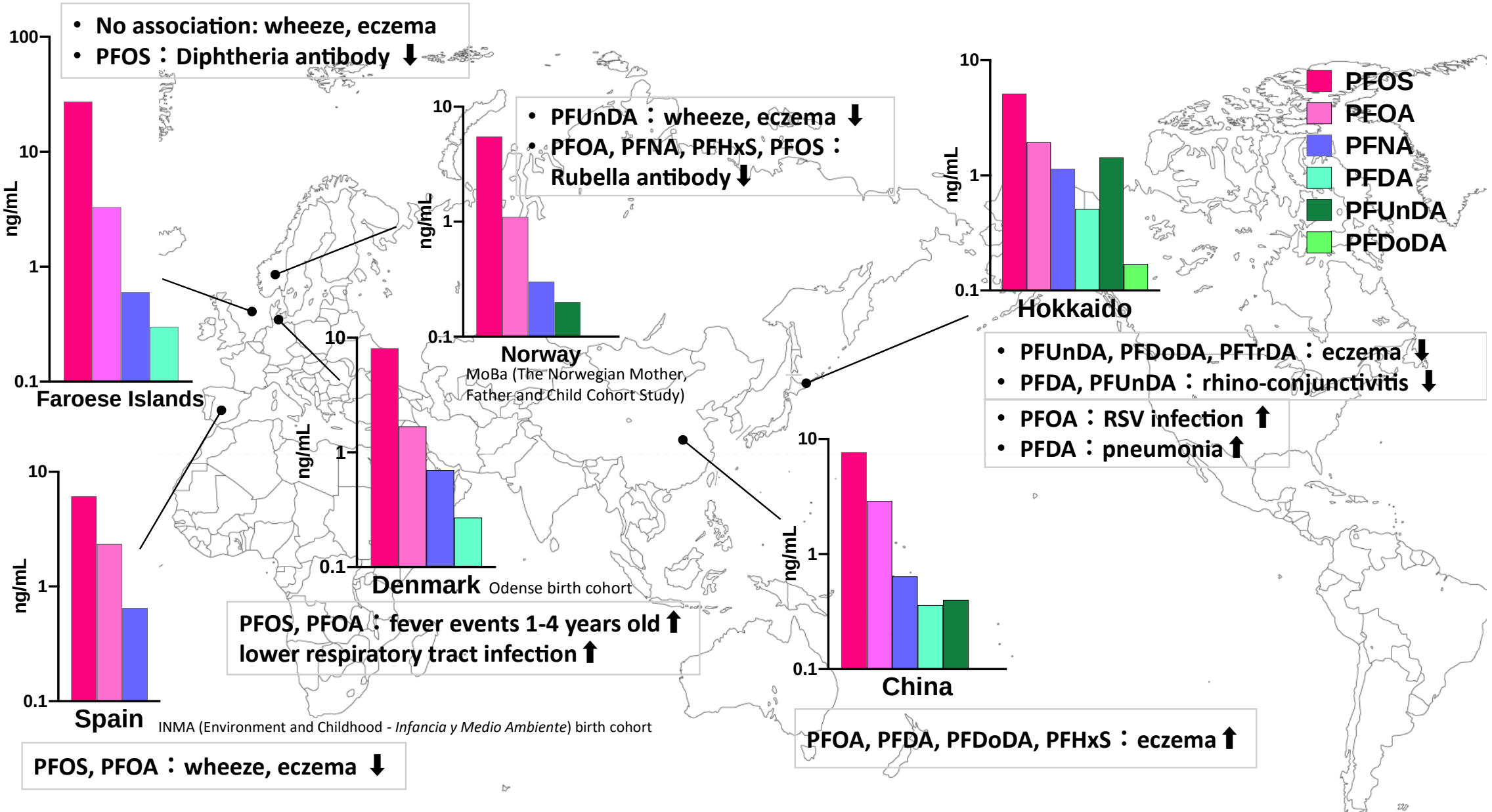




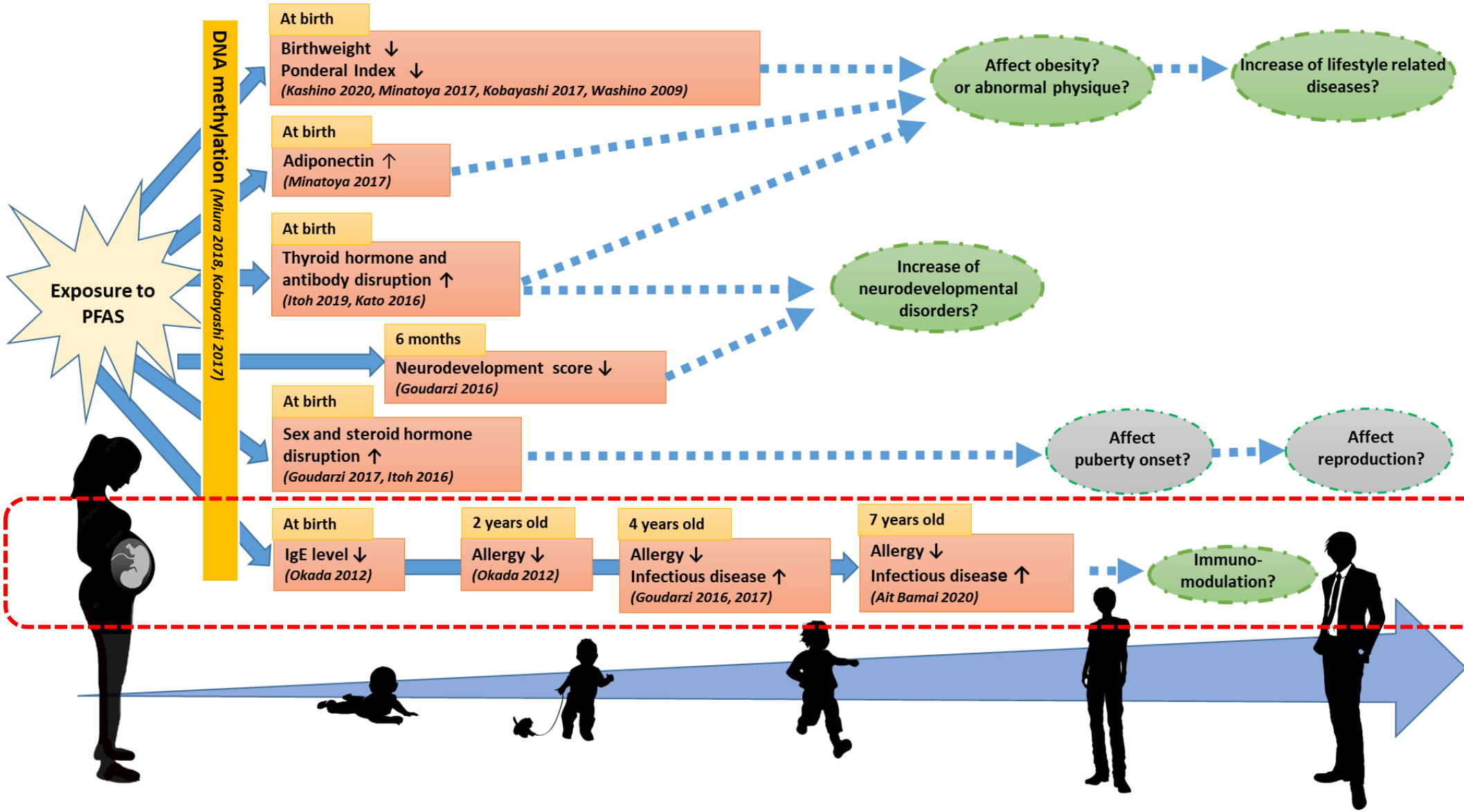


- Prenatal PFAS exposure reduced asthma and allergies, whereas increase infectious diseases
- *Immunosuppression (immunotoxicity) effects?*

Prenatal PFAS levels and childhood immune functions in different birth cohorts



How long the effect continue?



Further studies

1. **Long term follow-up**
2. **Examination of antibodies (*Diphtheria* and *Tetanus*)**

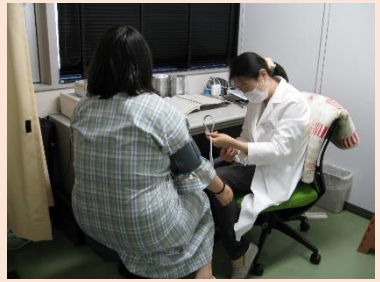
Children's face-to face examination (9-11y)

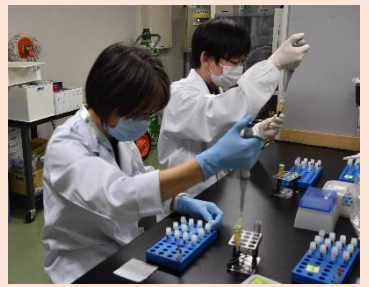
- Informed consent/assent
- Anthropometry measures
- FeNO (respiratory inflammations)
- Blood and urine sampling




Adolescents' face-to face examination (14-17y)

- Informed consent/assent
- Anthropometry measures,
- Tanner stage, blood pressure
- blood and urine sampling





in utero > At birth > childhood > **Adolescent** > Adult > Elderly

Now we are at this stage

Thank you very much for your kind attention!

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