

有機フッ素化合物と子どもの健康： 環境と健康に関する北海道スタディの結果から

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アウトライン

I. 背景：環境化学物質

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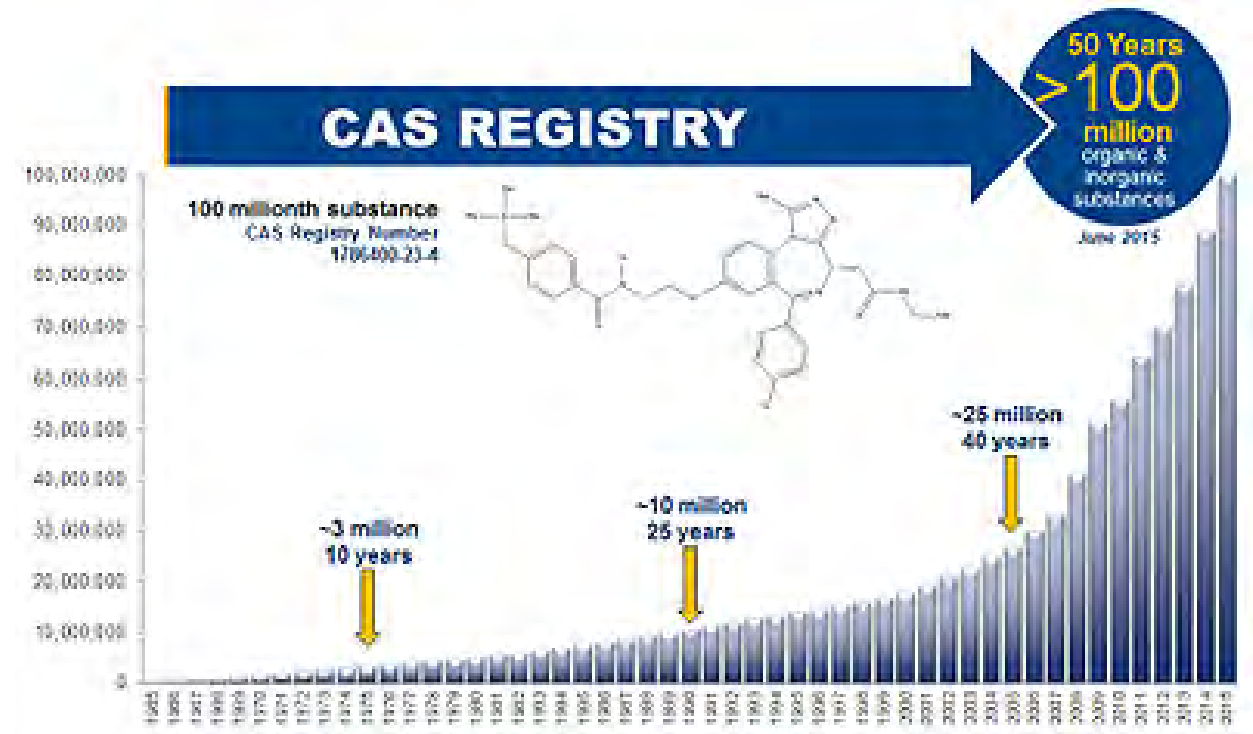
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研究の背景：合成化学物質の増加

- Chemical Abstract Service (CAS) 108059000 (www.cas.org)
- 2055 605,000 BACS 2015 C
- 100 millionth substance CAS Registry Number 1706400-21-4
- 3 million 10 years, 10 million 25 years, 26 million 40 years
- 2015 American Chemical Society



2015 American Chemical Society

有機フッ素化合物 Forever Chemicals (Per- and polyfluorinated alkyl substances : PFAS)

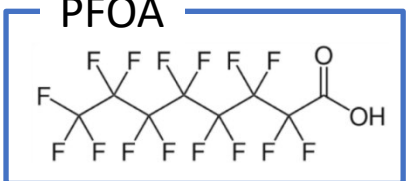
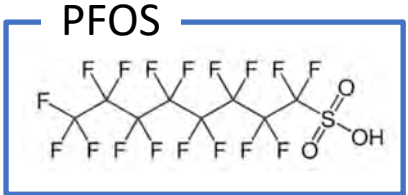
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” \¶ È\¹\• Ç ì Ô\Õ \hat \ç\lõ\l\Ã\® 8\¶ \- \õ\• „ V \Ù PFOS 5.4 « \• PFOA
3.8 « (Olsen et al. 2007)

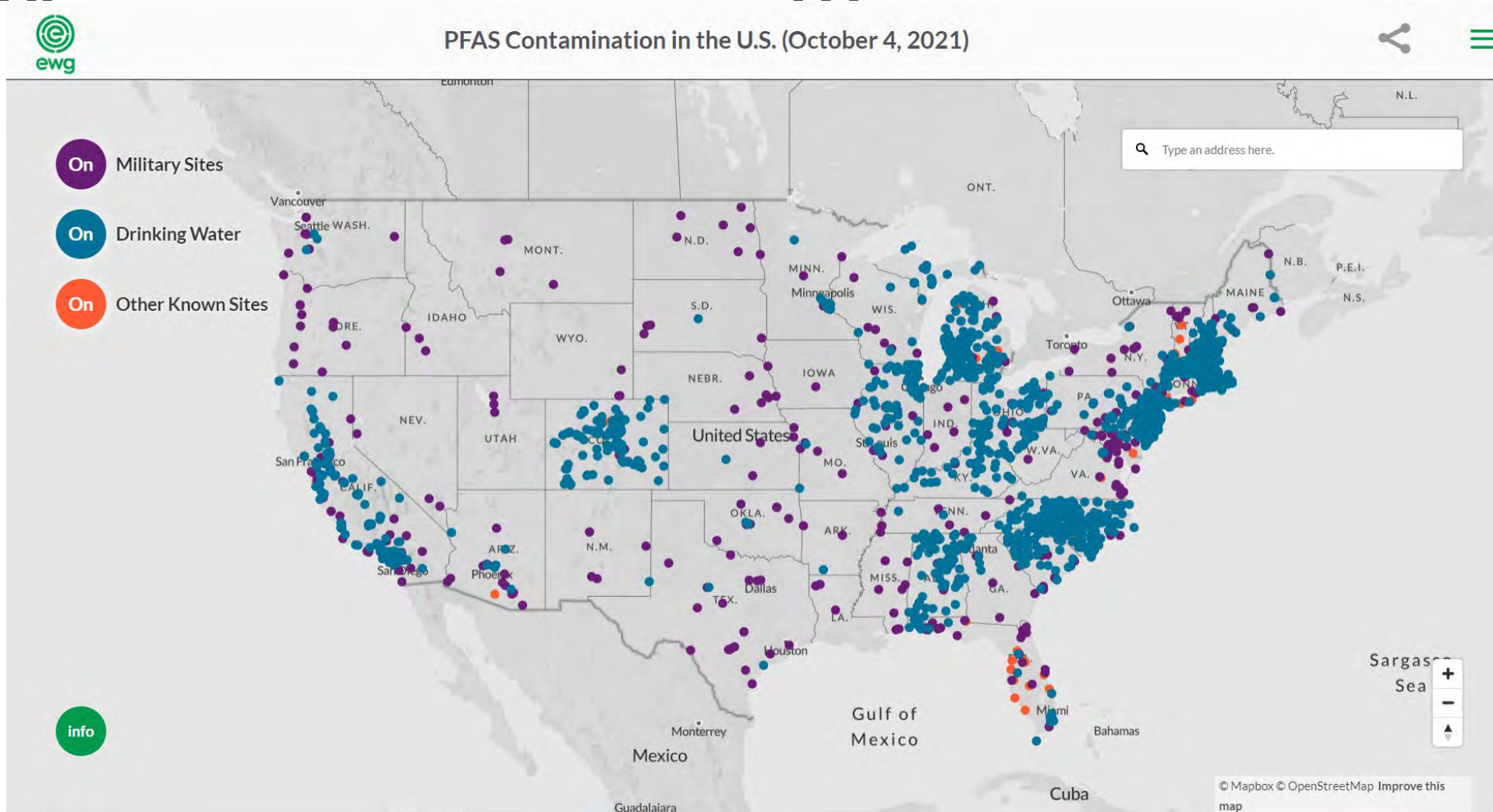
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2008; Halldorsson et al. 2008; Begley et al. 2005; Björklund et al. 2009)



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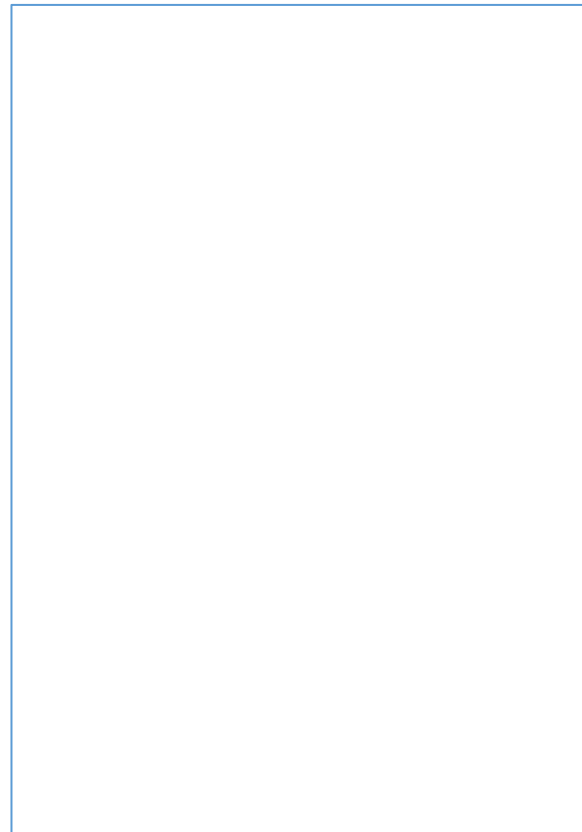
アメリカにおける汚染

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https://www.ewg.org/interactive-maps/pfas_contamination/map/

環境化学物質（外因性内分泌かく乱化学物質）



動物実験や高レベル曝露では、

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しかし、

一般的な環境レベルでの、ヒトへの影響は明らかになっていない

アウトライン

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II. 環境と子どもの健康に関する北海道スタディ

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環境と子どもの健康に関する北海道スタディ



2001年から2つのコホート研究を実施 (研究代表者 岸玲子)

	札幌コホート	北海道大規模コホート
リクルート	2001~2004年	2002~2012年
登録人数 (母)	514名 (札幌市1産科施設)	20,926名 (北海道37医療機関)

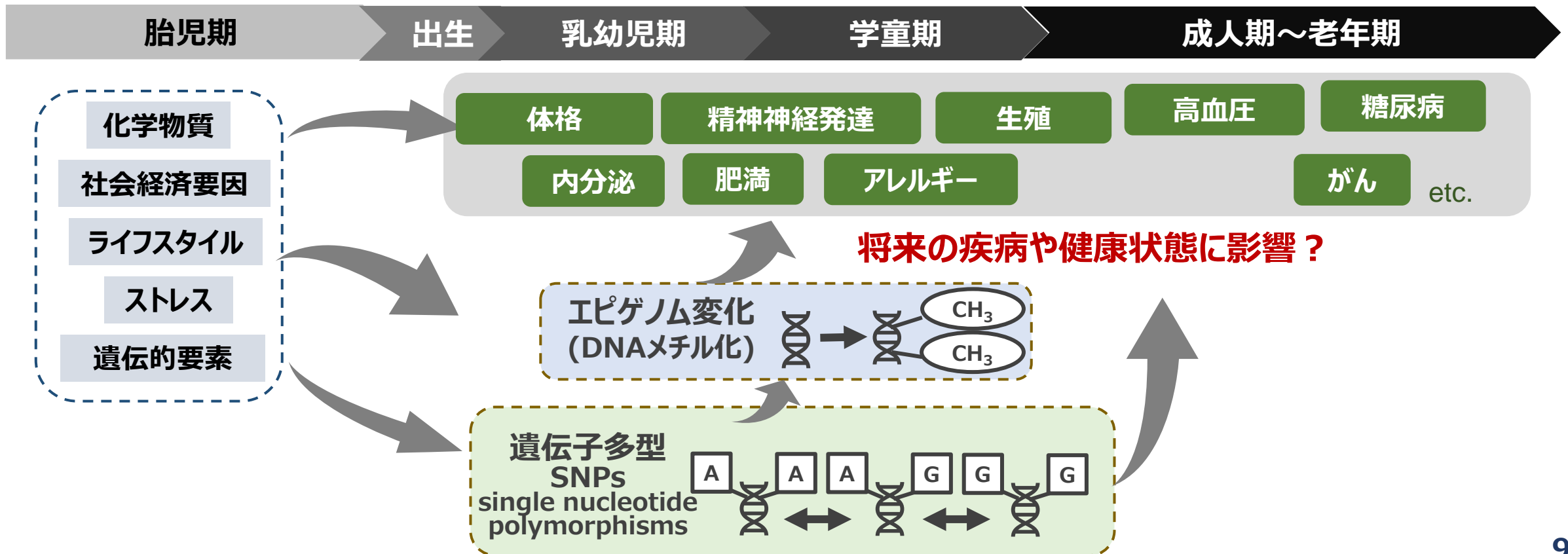
特徴

1. 低濃度の環境化学物質の次世代影響を解明
2. 母体血・臍帯血を保存、胎児期の環境曝露測定と生後の曝露評価
3. 先天異常、出生時体格、発育、神経行動発達、免疫・アレルギー、内分泌ホルモン等のリスク評価
4. 化学物質代謝や疾病感受性遺伝子などを考慮したハイリスク群の特定
(遺伝子多型SNPs)
5. エピゲノム解析を通じた環境遺伝相互作用やメカニズムの解明

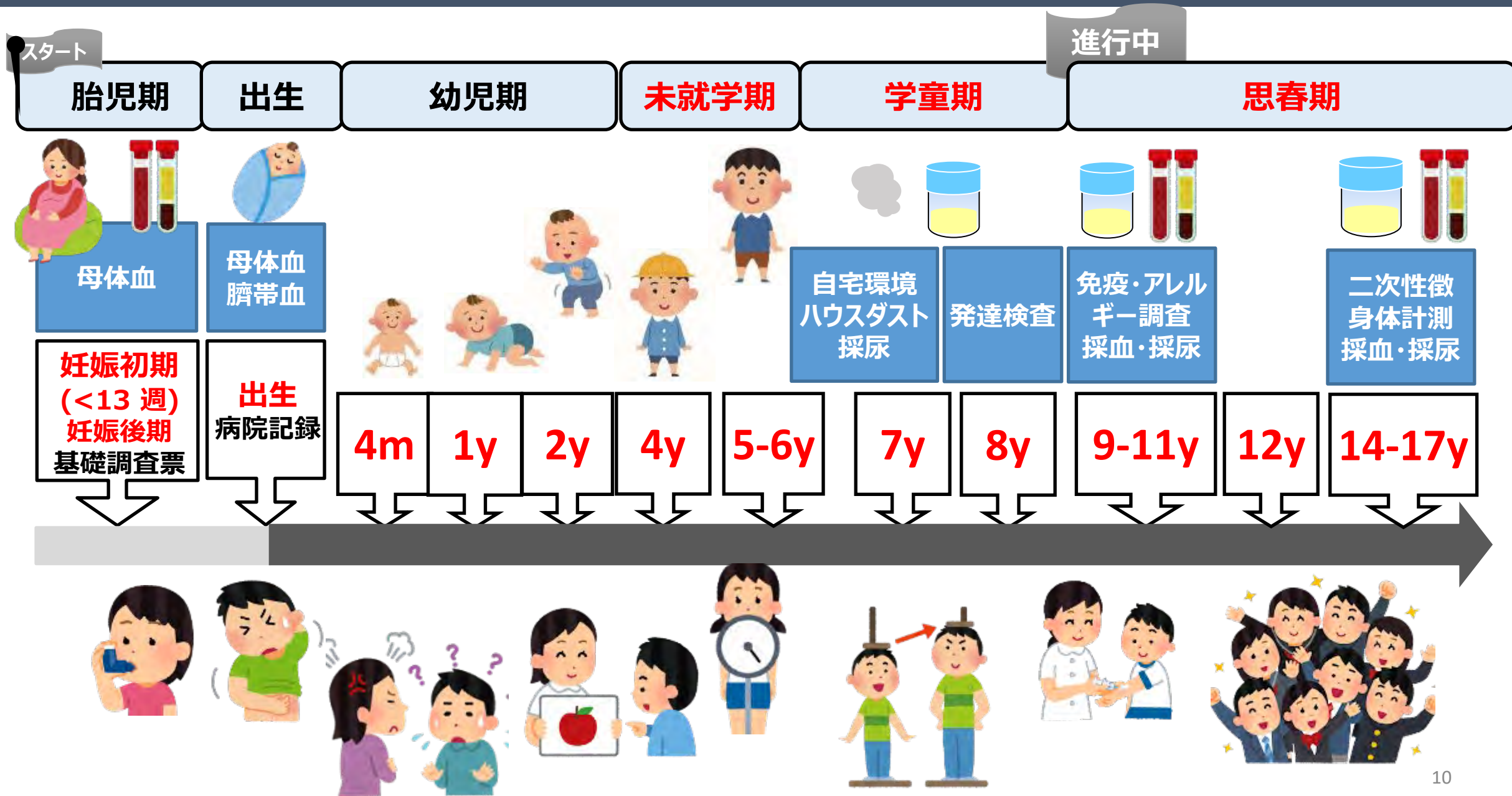
Developmental Origins of Health and Disease: DOHaD

1. 将来の健康や特定の病気へのかかりやすさは、胎児期や生後早期の環境の影響を強く受けて決定される
2. 同じ環境でも将来の疾病や健康状態には個人差（感受性）がある
3. 環境によるエピゲノム変化が将来の疾病や健康状態を規定する

出生コホート研究の長期追跡によって実現するライフコースアプローチ



研究の流れ



研究で測定している化学物質

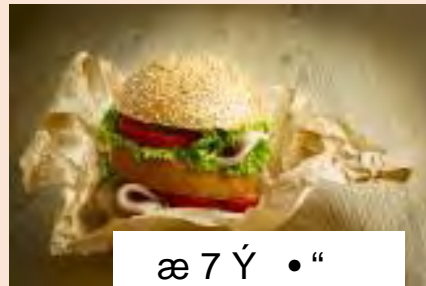
残留性有機汚染物質

(すでに一部規制されているが、環境中に残っている)

- 塩素系農薬 (DDTなど)
- ダイオキシン
- 塩素系難燃剤PCB類
- **有機フッ素化合物 (PFAS)**



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PCB , ÿ

短半減期物質

(日用品に使用されている)

- フタル酸エステル類
- ビスフェノール類
- リン系難燃剤PFR類



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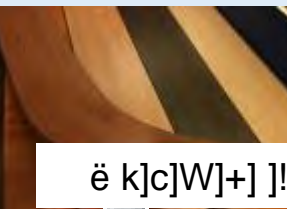
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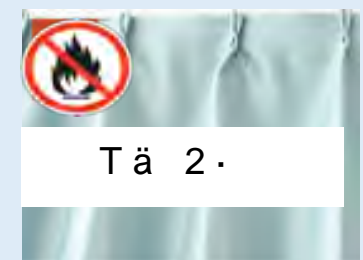
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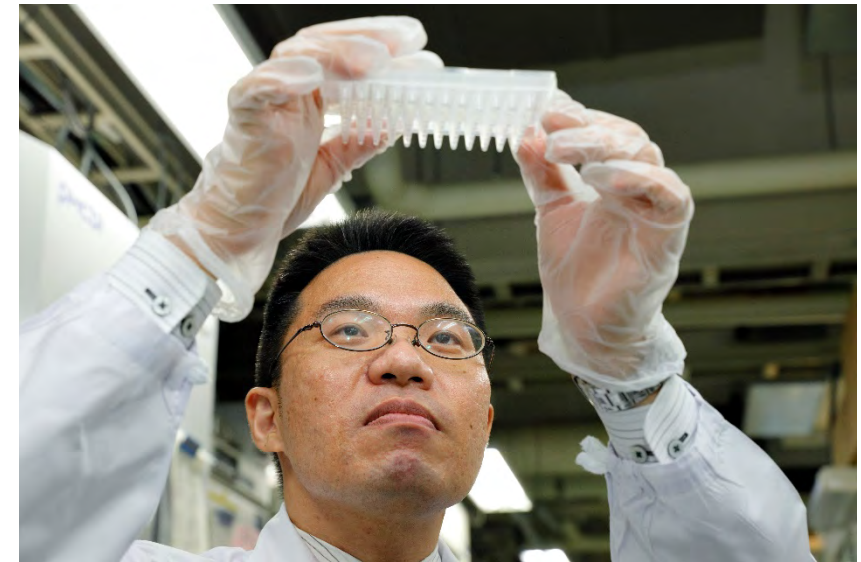


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その他の測定項目

項目	試料
コチニン*	母体血
葉酸*	母体血
脂肪酸、トリグリセリド**	母体血
IgE, IgA**	臍帯血
甲状腺ホルモン: TSH, fT4, fT3*	母体血、臍帯血
ステロイドホルモン、性ホルモン (LH, FSH, SHBG, Inhibin B, INSL3、プロラクチン)	臍帯血
遺伝子 (SNPs, DNAメチル化)	母体血、臍帯血

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これまでに報告した（健康）アウトカムと要因

健康（アウトカム）	関連する要因（Journal name, year）
出生アウトカム・体格	たばこ (Cotinine) (BMJ Oepn, 2019) , カフェイン (Pediatric Res, 2017) , 葉酸 (Brit J Nutrit ; JE2019) , 教育歴, BMI (IJERPH, 2018; Matern. Child Health J, 2021), Risk score (Clin Pediat Endocrinol, 2019) 、ステロイドホルモン (Am J Human Biol、2018) ダイオキシン (Environ Res, 2009), 有機フッ素化合物 (EHP, 2009; JESEE, 2017, Env Int 2020), 水銀 (STOTEN, 2015) , フタル酸エステル類 (STOTEN, 2017) , 妊娠高血圧 (IJERPH, 2021; IJERPH, 2021)
甲状腺ホルモン	有機フッ素化合物 (EHPM, 2016; Environ Int, 2019) , ダイオキシン (STOTEN, 2018) 、OH-PCB (Environ Res 2018) , 塩素系農薬 (Env Res 2020)
性ホルモン、アディポカイン、性的二型	有機フッ素化合物 (Environ Int, 2016; EHP, 2017; Environ Res, 2017; Environ Int 2022) , フタル酸エステル類 (PLOS One, 2014; STOTEN, 2017) , ビスフェノール A (Epidemiology, 2017) , 塩素系農薬 (Environ Int, 2018) , ダイオキシン (Environ Int, 2018) 、性ホルモン (PLOS One 2015; Pediatr Int, 2019)
精神神経発達	社会経済要因 (IEA, 2014; Child Care Health Dev, 2017, Pediatr Int 2020) , ダイオキシン (EHP, 2006; Environ Res, 2017; STOTEN, 2018) , 塩素系農薬 (Neurotoxicology, 2018), 有機フッ素化合物 (STOTEN, 2016) , ビスフェノール A (STOTEN, 2018) , Adipokines (IJERPH, 2018)
喘息アレルギー、免疫	ダイオキシン (Environ Res, 2011; STOTEN, 2018) 、有機フッ素化合物 (Environ Res, 2012; Environ Int, 2014, 2016, 2017, 2021) 、フタル酸エステル類 (STOTEN, 2018; Environ int 2022) 、リン系難燃剤(Environ Int, 2019)
遺伝環境相互作用	たばこ (Mol Human Reprod, 2006; Am J Epidemiol, 2008; J Epidemiol, 2012; Toxicol Lett, 2013; Reproduc Toxicol, 2016; STOTEN, 2017) , 性的二型 (Steroid, 2019) , フタル酸エステル類、ビスフェノール A (Steroid 2020) , PFASと脂肪酸 (Reprod toxicol, 2022)
エピゲノム	たばこ (Sci Rep, 2018) , たばことADHD (Clin Epigenetics, 2021), 葉酸とアレルギー (Ped Allerg Immunol, 2021), 有機フッ素化合物 (JESEE, 2018; Environ Int, 2018), ビスフェノール A (Sci Rep, 2019) 、フタル酸エステル類 (STOTEN, 2021)
曝露レベルと傾向変動	有機フッ素化合物 (EI 2014; IJPREH), フタル酸エステル類 (IJHPH, 2021), ビスフェノール A (Env Res 2020), リン系難燃剤 (IJHEH 2020)

アウトライン

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III. 有機フッ素化合物の結果を中心に

① 曝露レベルと母の特徴との関連

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The Hokkaido Birth Cohort Study on Environment and Children's Health: cohort profile—updated 2017

Reiko Kishi^{1*}, Atsuko Araki¹, Machiko Minatoya¹, Tomoyuki Hanaoka¹, Chihiro Miyashita¹, Sachiko Itoh¹, Sumitaka Kobayashi¹, Yu Ait Bamai¹, Keiko Yamazaki¹, Ryu Miura¹, Naomi Tamura^{1,2}, Kumiko Ito^{1,3}, Houman Goudarzi^{1,4} and the members of The Hokkaido Study on Environment and Children's Health

化学物質の曝露レベル

PFOSは100%、PFOAは93%の母体血から検出

Table 6 Exposure levels of environmental chemicals in the Sapporo cohort

	Number	DL	>DL (%)	Min	Percentile			Max
					25th	50th	75th	
Maternal blood								
Total dioxins (TEQ pg/g lipid)	426	n/a	n/a	3.17	9.95	13.9	18.2	43.4
Total PCBs (ng/g lipid)	426	n/a	n/a	17.8	73.0	107	148	41,460
<i>p,p'</i> -DDE	379	0.60	100	99.52	401.53	650.99	1011.48	4575.67
PFOS (ng/mL)	447	0.5	100	1.30	3.40	5.20	7.00	16.2
PFOA (ng/mL)	447	0.5	92.8	0.25	0.80	1.30	1.80	5.30
MEHP (ng/mL)	493	0.278	100	1.94	5.82	9.95	16.3	101.7
Bisphenol A (ng/mL)	59	0.04	76.3	<DL	0.040	0.057	0.072	0.419
Cord blood								
Bisphenol A (ng/mL)	285	0.04	68.8	<DL	<DL	0.051	0.076	0.217
Maternal hair								
Me-Hg (μg/g)	430	n/a	100	0.24	0.96	1.40	1.89	7.55

p,p'-DDE *p,p'*-dichlorodipenyldichloroethylene, DL detection limit, Me-Hg methylmercury, MEHP mono(2-ethylhexyl) phthalate, n/a not applicable, PCBs polychlorinated biphenyls, PFOA perfluorooctanoic acid, PFOS perfluorooctanoic sulfonate, TEQ toxicity equivalency quantity



母体血および臍帯血中のPFOS、PFOA濃度 (ng/mL)

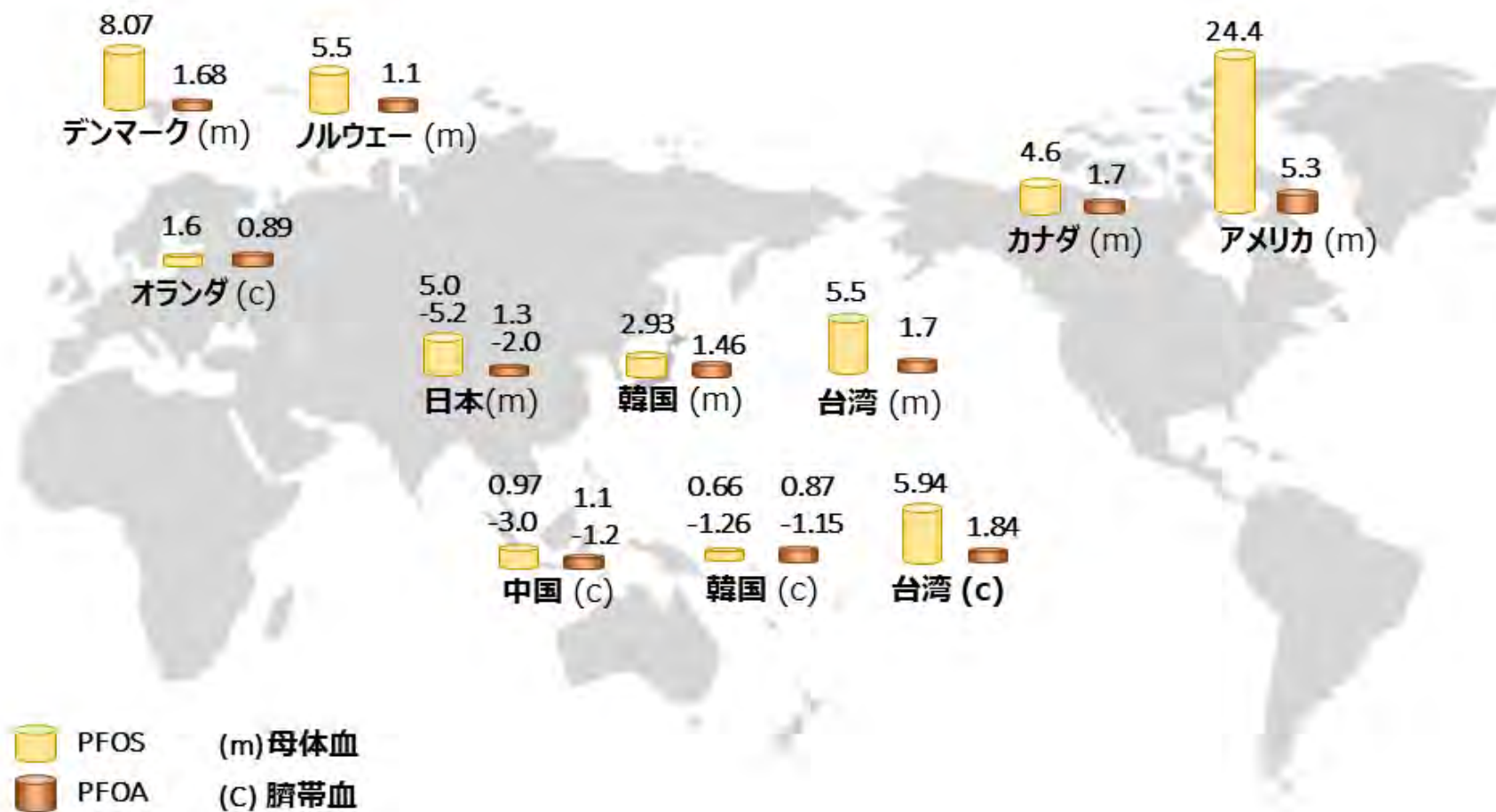
Birth cohorts in Asia: The importance, advantages, and disadvantages of different-sized cohorts



Reiko Kishi ^{a,*}, Atsuko Araki ^a, Machiko Minatoya ^a, Sachiko Itoh ^a, Houman Goudarzi ^{a,b}, Chihiro Miyashita ^a

^a Center for Environmental and Health Sciences, Hokkaido University, Sapporo, Japan

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Article

Determinants and Temporal Trends of Perfluoroalkyl Substances in Pregnant Women: The Hokkaido Study on Environment and Children's Health

Meng-Shan Tsai ^{1,2,3}, Chihiro Miyashita ¹, Atsuko Araki ^{1,2}, Sachiko Itoh ¹, Yu Ait Bamai ¹, Houman Goudarzi ^{1,4}, Emiko Okada ⁵, Ikuko Kashino ⁵, Hideyuki Matsuura ⁶ and Reiko Kishi ^{1,*}

北海道コ-ホ-ト母体血中 PFAS濃度 (ng/mL)

Table 2. Distribution of 11 PFAS in plasma from pregnant women.

	MDL ^a	n	%	GM	Mean	Min	25th	50th	75th	Max
PFHxS (C6)	0.2	1732	81.54	0.34	0.37	<0.2	0.26	0.33	0.42	3.39
PFHxA (C6)	0.1	976	45.95	0.16	0.16	<0.1	<0.1	<0.1	0.18	0.69
PFHpA (C7)	0.1	740	34.84	0.16	0.18	<0.1	<0.1	<0.1	0.20	1.02
PFOS (C8)	0.3	2123	99.95	4.96	5.74	0.81	3.66	4.96	6.79	30.28
PFOA (C8)	0.2	2123	99.95	2.06	2.64	0.25	1.29	2.00	3.24	24.88
PFNA (C9)	0.3	2121	99.86	1.19	1.35	0.32	0.87	1.15	1.57	13.19
PFDA (C10)	0.1	2110	99.34	0.51	0.57	<0.1	0.39	0.52	0.69	2.43
PFUnDA (C11)	0.1	2117	99.67	1.35	1.50	0.11	1.02	1.40	1.87	5.89
PFDoDA (C12)	0.1	1915	90.16	0.19	0.21	<0.1	0.15	0.19	0.24	0.73
PFTTrDA (C13)	0.1	2073	97.60	0.32	0.35	<0.1	0.25	0.33	0.42	1.33
PFTeDA (C14)	0.1	308	14.50	0.12	0.12	<0.1	<0.1	<0.1	<0.1	0.30

PFHxS, perfluorohexane sulfonate; PFHxA, perfluorohexanoic acid; PFHpA, perfluoroheptanoic acid; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFUnDA, perfluoroundecanoic acid; PFDoDA, perfluoro-dodecanoic acid; PFTTrDA, perfluorotridecanoic acid; PFTeDA, perfluorotetradecanoic acid. ^a MDL: method detection limit.

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ng/mL	PFOS	PFOA	PFHxS
ä Ù Ó Ø	13.7	3.2	16.4
µ Ø	5.6	2.6	3.4
, • Ø 1981 «	27.9	17.3	22.7
\Ç\Ø N	10.2	4.6	6.8

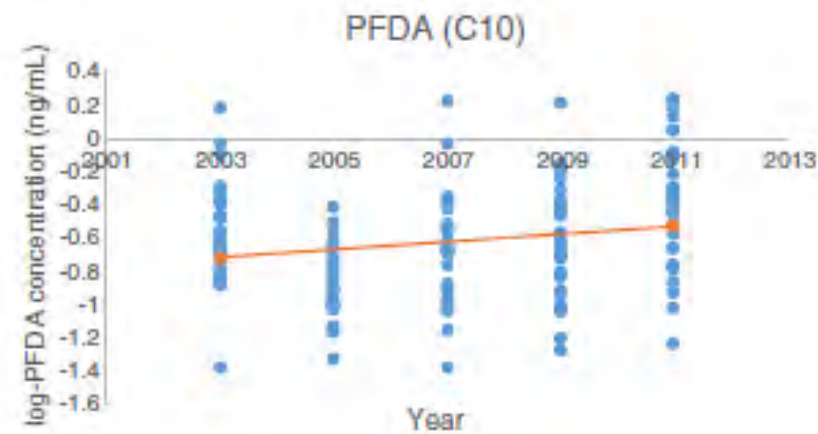
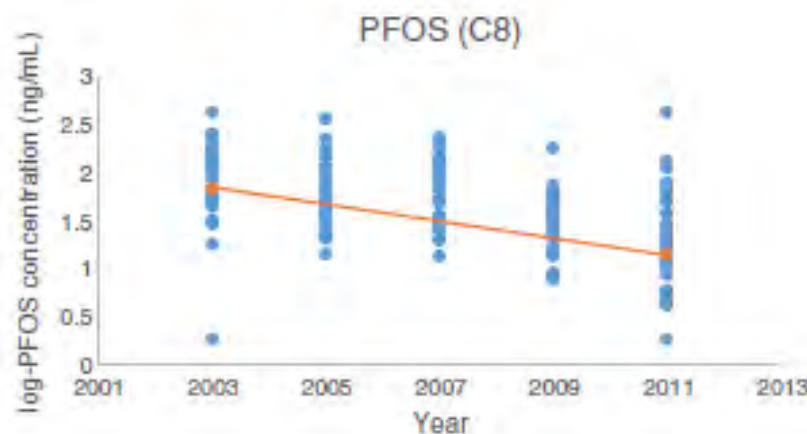
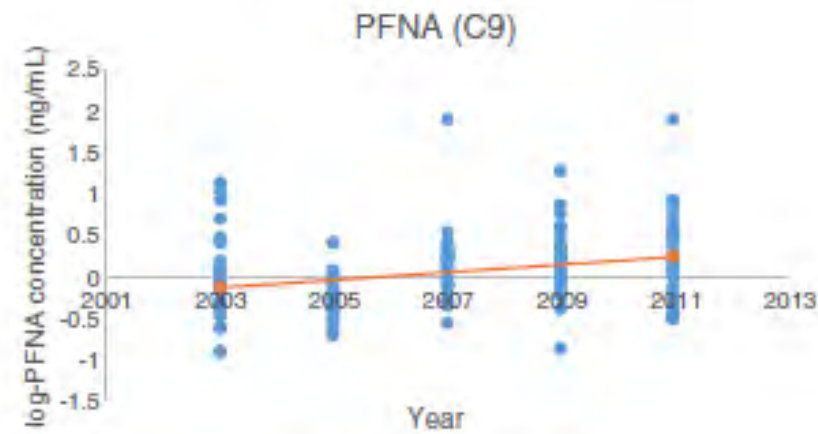
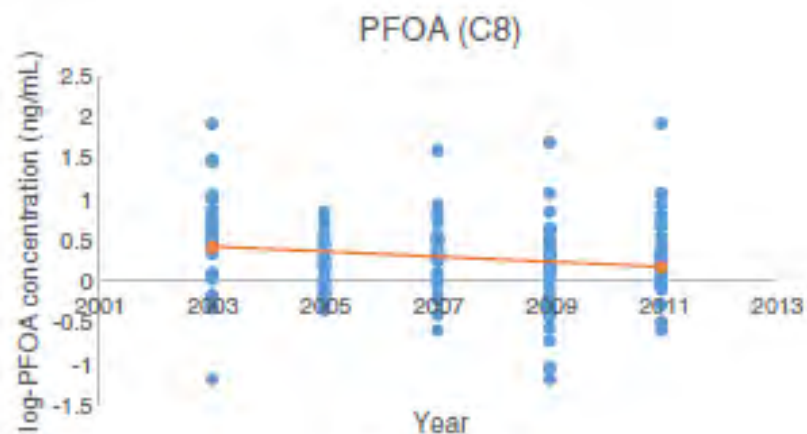


母体血中PFAS濃度の 長期的傾向 (2003年～2011年)

Temporal trends of perfluoroalkyl acids in plasma samples of pregnant women in Hokkaido, Japan, 2003–2011 ☆☆☆

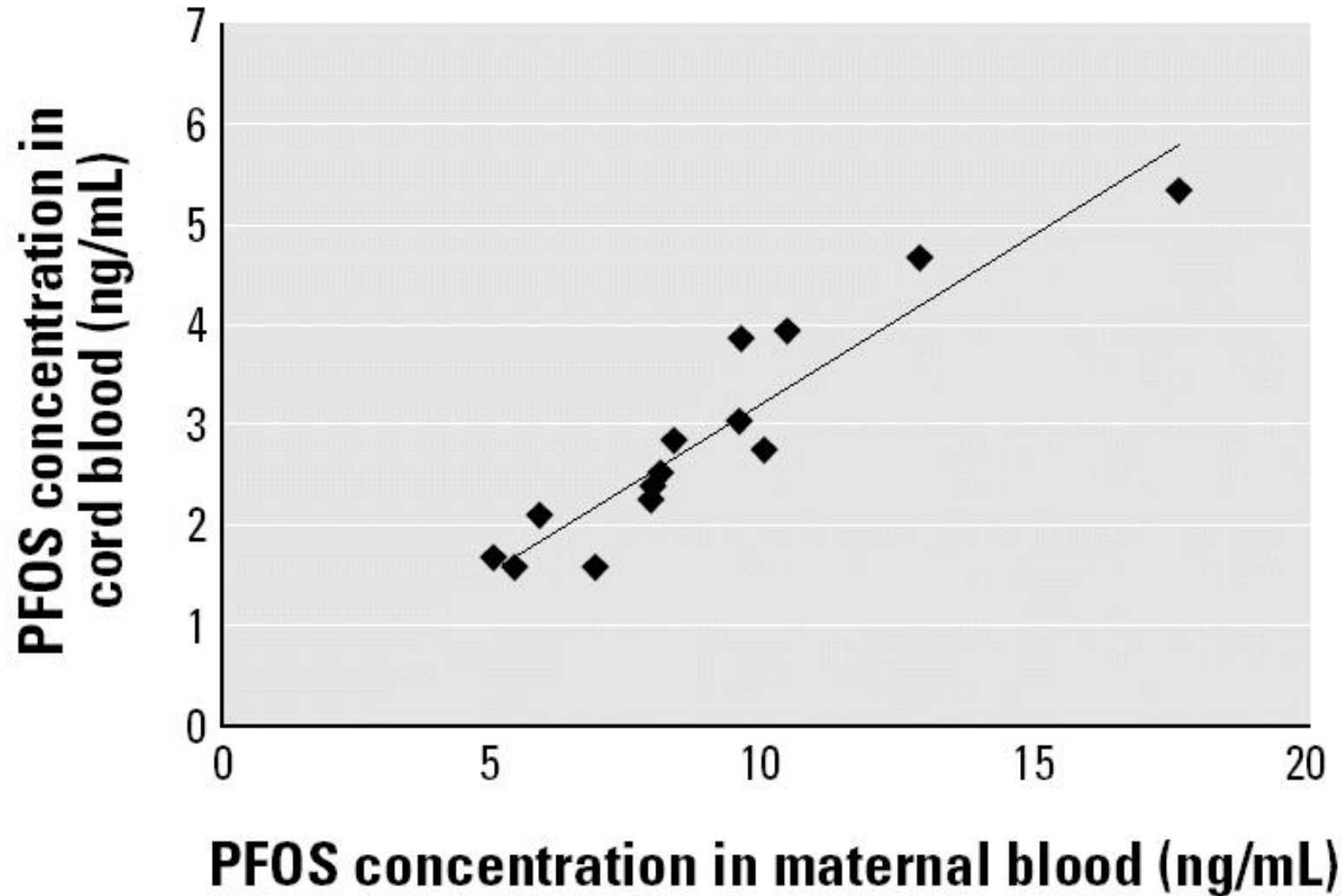


Emiko Okada ^a, Ikuko Kashino ^a, Hideyuki Matsuura ^b, Seiko Sasaki ^a, Chihiro Miyashita ^c, Jun Yamamoto ^d, Tamiko Ikeno ^c, Yoichi M. Ito ^e, Toru Matsumura ^c, Akiko Tamakoshi ^a, Reiko Kishi ^{c,*}



- PFOS, PFOA, PFNA, PFDA, PFDAFy * W
- PFNA, PFDA, PFDAFy V ¼

母体血から臍帯血への移行（濃度相関は直線的）



Demographic, behavioral, dietary, and socioeconomic characteristics related to persistent organic pollutants and mercury levels in pregnant women in Japan



Chihiro Miyashita^a, Seiko Sasaki^b, Yasuaki Saijo^c, Emiko Okada^b, Sumitaka Kobayashi^b, Toshiaki Baba^b, Jumboku Kajiwara^d, Takashi Todaka^e, Yusuke Iwasaki^f, Hiroyuki Nakazawa^f, Noriyuki Hachiya^g, Akira Yasutake^h, Katsuyuki Murataⁱ, Reiko Kishi^{a,*}

母体血中PFOS、PFOA濃度と関連する因子

- PFOS、PFOA : 初産婦 > 経産婦、妊娠中 > 妊娠後
- PFOS : 非喫煙者 > 喫煙者
- PFOS、PFOA : 妊娠週数が経過すると低くなる

母体血中PFAS（11化合物）と 関連する因子

Determinants and Temporal Trends of Perfluoroalkyl Substances in Pregnant Women: The Hokkaido Study on Environment and Children's Health


Meng-Shan Tsai ^{1,2,3}, Chihiro Miyashita ¹, Atsuko Araki ^{1,2} , Sachiko Itoh ¹, Yu Ait Bamai ¹, Houman Goudarzi ^{1,4}, Emiko Okada ⁵, Ikuko Kashino ⁵, Hideyuki Matsuura ⁶ and Reiko Kishi ^{1,*}

Table 4. Adjust regression coefficients (β) and 95% confidence intervals in multivariable linear regression model by PFAS in pregnant women.

	PFHxS	PFOS	PFOA	PFNA	PFDA	PFUnDA	PFDoDA	PFTTrDA
Age at delivery (years)								
<25	ref	ref	ref	ref	ref	ref	ref	ref
25–29	0.071 (−0.026, 0.169)	0.114 (0.036, 0.191)	−0.028 (−0.136, 0.081)	0.006 (−0.072, 0.085)	0.014 (−0.07, 0.098)	0.103 (0.015, 0.191)	0.046 (−0.04, 0.132)	0.02 (−0.063, 0.104)
30–34	0.028 (−0.068, 0.124)	0.026 (−0.05, 0.103)	−0.049 (−0.156, 0.058)	0.019 (−0.058, 0.097)	0.012 (−0.07, 0.095)	0.118 (0.031, 0.205)	0.088 (0.003, 0.173)	0.063 (−0.02, 0.145)
≥35	0.054 (−0.051, 0.159)	0.064 (−0.02, 0.148)	−0.038 (−0.156, 0.079)	0.041 (−0.044, 0.126)	0.046 (−0.044, 0.136)	0.131 (0.036, 0.227)	0.071 (−0.022, 0.164)	0.078 (−0.012, 0.168)
<i>p</i> for trend	0.895	0.574	0.498	0.224	0.272	0.025	0.094	0.026
Prepregnancy BMI								
<18.5	−0.032 (−0.096, 0.032)	0.034 (−0.018, 0.085)	0.001 (−0.071, 0.072)	0.058 (0.006, 0.11)	0.033 (−0.022, 0.089)	0.035 (−0.023, 0.094)	0.056 (−0.001, 0.113)	0.037 (−0.018, 0.092)
18.5–24.9	ref	ref	ref	ref	ref	ref	ref	ref
≥25	0.021 (−0.067, 0.109)	−0.036 (−0.107, 0.034)	−0.034 (−0.133, 0.064)	−0.012 (−0.083, 0.06)	−0.015 (−0.091, 0.061)	−0.07 (−0.15, 0.009)	−0.166 (−0.244, −0.088)	−0.162 (−0.238, −0.087)
<i>p</i> for trend								
Parity								
0	ref	ref	ref	ref	ref	ref	ref	ref
1	−0.225 (−0.28, −0.17)	−0.172 (−0.216, −0.127)	−0.447 (−0.508, −0.386)	−0.201 (−0.245, −0.156)	−0.106 (−0.153, −0.059)	0.015 (−0.035, 0.065)	0.006 (−0.043, 0.054)	0.005 (−0.042, 0.052)
≥2	−0.233 (−0.305, −0.16)	−0.286 (−0.344, −0.227)	−0.621 (−0.702, −0.54)	−0.271 (−0.33, −0.212)	−0.135 (−0.197, −0.072)	0.025 (−0.042, 0.091)	−0.007 (−0.071, 0.058)	0.021 (−0.042, 0.083)
<i>p</i> for trend	<0.001	<0.001	<0.001	<0.001	<0.001	0.382	0.922	0.582
Education level (years)								
≤9	ref	ref	ref	ref	ref	ref	ref	ref
10–12	−0.145 (−0.291, 0.002)	0.106 (−0.011, 0.224)	−0.173 (−0.337, −0.01)	0.058 (−0.061, 0.176)	0.159 (0.033, 0.285)	0.212 (0.079, 0.345)	0.077 (−0.052, 0.207)	0.067 (−0.059, 0.192)
13–16	−0.087 (−0.234, 0.061)	0.122 (0.003, 0.24)	−0.133 (−0.297, 0.031)	0.099 (−0.021, 0.218)	0.208 (0.081, 0.335)	0.265 (0.131, 0.399)	0.122 (−0.008, 0.253)	0.117 (−0.01, 0.243)
>16	0.016 (−0.145, 0.177)	0.229 (0.1, 0.358)	−0.007 (−0.187, 0.172)	0.218 (0.088, 0.349)	0.267 (0.128, 0.406)	0.322 (0.176, 0.468)	0.155 (0.013, 0.298)	0.106 (−0.032, 0.244)
<i>p</i> for trend	0.004	<0.001	0.022	<0.001	<0.001	<0.001	0.005	0.032
Cotinine Level in 3rd trimester								
Non-smoker (<0.22 ng/mL)	ref	ref	ref	ref	ref	ref	ref	ref
Passive smoker (0.22–11.49 ng/mL)	−0.007 (−0.059, 0.046)	0.069 (0.027, 0.111)	0.060 (0.002, 0.119)	−0.004 (−0.047, 0.038)	−0.002 (−0.047, 0.043)	0.015 (−0.033, 0.062)	−0.01 (−0.057, 0.036)	0.026 (−0.019, 0.071)
Active smoker (>11.49 ng/mL)	0.068 (−0.028, 0.163)	0.034 (−0.042, 0.11)	0.104 (−0.003, 0.210)	−0.043 (−0.121, 0.034)	−0.049 (−0.132, 0.033)	−0.111 (−0.198, −0.025)	−0.059 (−0.143, 0.026)	0.015 (−0.066, 0.097)
<i>p</i> for trend	0.43	0.019	0.021	0.398	0.404	0.176	0.248	0.381
Alcohol consumption history								
No	ref	ref	ref	ref	ref	ref	ref	ref
Yes	0.012 (−0.013, 0.037)	0.002 (−0.018, 0.022)	0.012 (−0.015, 0.04)	−0.008 (−0.028, 0.012)	−0.027 (−0.048, −0.006)	−0.019 (−0.041, 0.004)	−0.011 (−0.033, 0.011)	0.001 (−0.021, 0.022)
Annual housed income (million yen)								
<3	ref	ref	ref	ref	ref	ref	ref	ref
3–5	−0.007 (−0.074, 0.059)	0.039 (−0.015, 0.092)	0.015 (−0.059, 0.089)	0.027 (−0.026, 0.081)	0.045 (−0.012, 0.102)	0.019 (−0.041, 0.08)	0.014 (−0.045, 0.072)	−0.016 (−0.073, 0.041)
>5	0.064 (−0.008, 0.136)	0.094 (0.036, 0.152)	0.111 (0.031, 0.191)	0.08 (0.022, 0.139)	0.052 (−0.01, 0.114)	0.034 (−0.031, 0.1)	0.025 (−0.039, 0.089)	0.012 (−0.049, 0.074)
<i>p</i> for trend	0.041	0.001	0.003	0.004	0.127	0.304	0.438	0.565

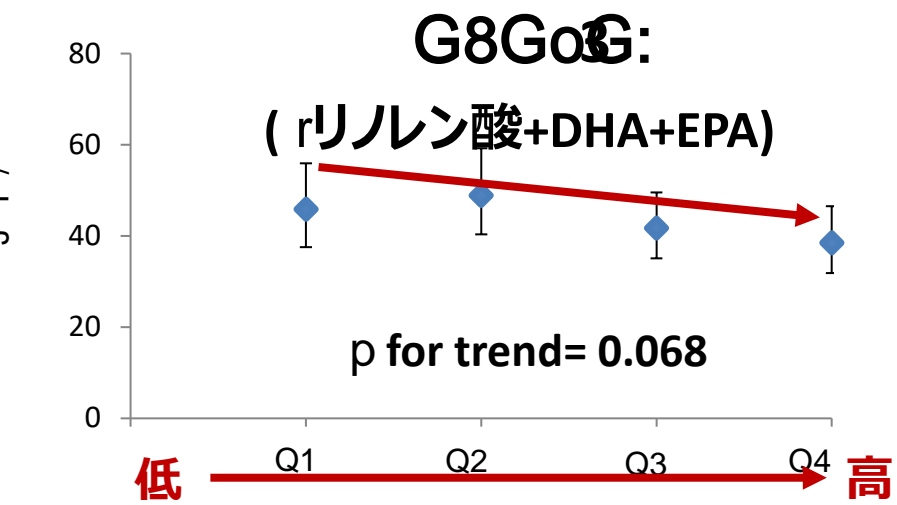
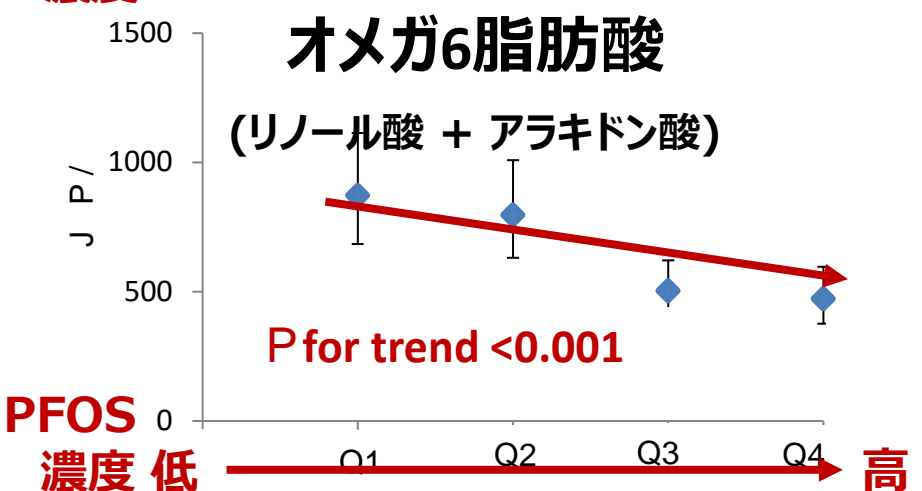
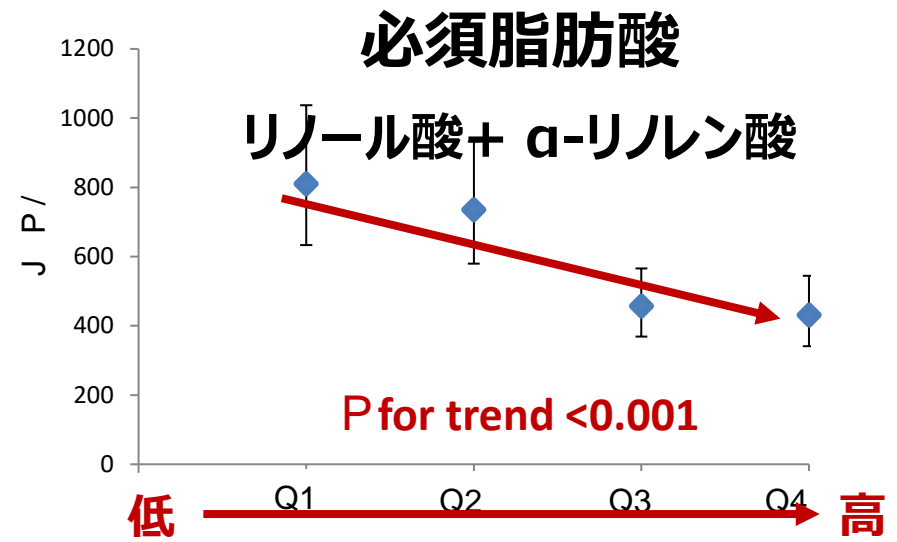
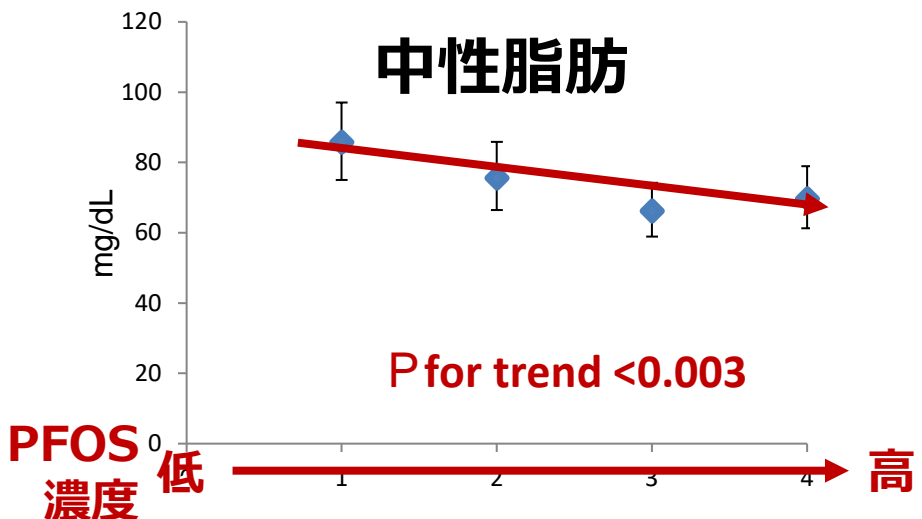
PFHxS, perfluorohexane sulfonate; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFUnDA, perfluoroundecanoic acid; PFDoDA, perfluorododecanoic acid; PFTTrDA, perfluorotridecanoic acid; BMI, body mass index; Model was adjusted for pre-pregnancy BMI, maternal education, annual housed income, parity, and age at delivery without itself; Bold represented *p* value < 0.05.

- 高学歴 > 低学歴
- 低BMI > 高BMI
- 高収入 > 低収入
- 飲酒なし > あり
- PFOA : 喫煙者 > 非喫煙者
- PFUnDA : 非喫煙者 > 喫煙者

The Association of Prenatal Exposure to Perfluorinated Chemicals with Maternal Essential and Long-Chain Polyunsaturated Fatty Acids during Pregnancy and the Birth Weight of Their Offspring: The Hokkaido Study

Reiko Kishi,¹ Tamie Nakajima,^{2,3} Houman Goudarzi,¹ Sachiko Kobayashi,¹ Seiko Sasaki,⁴ Emiko Okada,⁴ Chihiro Miyashita,¹ Sachiko Itoh,¹ Atsuko Araki,¹ Tamiko Ikeno,¹ Yusuke Iwasaki,⁵ and Hiroyuki Nakazawa⁵

母体血中のPFOSと脂肪酸の逆相関



PFOS濃度が高いと母の栄養素が低い

Y

胎児への影響は？

adjusted for maternal age, smoking and alcohol intake during pregnancy, annual household income, parity and the blood sampling period (categorical).

アウトライン

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PFOSは女児の出生体重を下げる (札幌コーホート)

Correlations between Prenatal Exposure to Perfluorinated Chemicals and Reduced Fetal Growth

Noriaki Washino,¹ Yasuaki Saijo,² Seiko Sasaki,¹ Shizue Kato,¹ Susumu Ban,¹ Kanae Konishi,¹ Rie Ito,³ Ayako Nakata,³ Yusuke Iwasaki,³ Koichi Saito,³ Hiroyuki Nakazawa,³ and Reiko Kishi¹

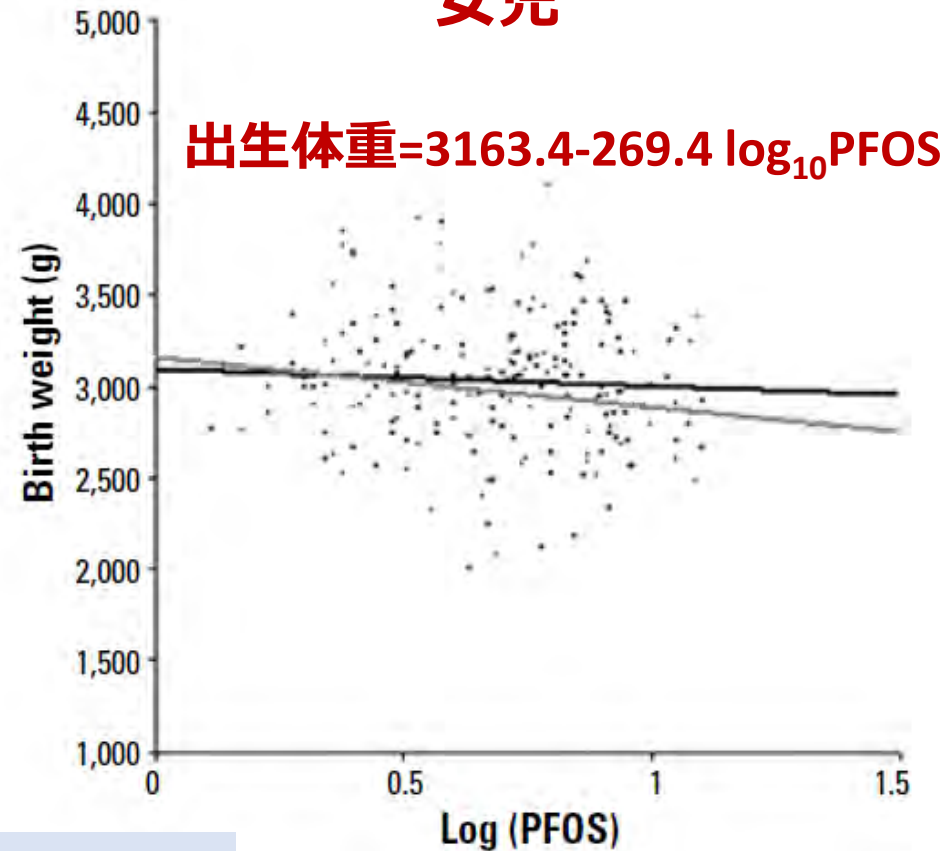
¹Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo, Japan; ²Department of Health Science, Asahikawa Medical College, Asahikawa, Japan; ³Department of Analytical Chemistry, Faculty of Pharmaceutical Sciences, Hoshi University, Tokyo, Japan

男女とも

Dependent variable	Partial regression coefficient of log ₁₀ PFOS (95%CI)	p-Value	Partial regression coefficient of log ₁₀ PFOA (95%CI)	p-Value
Birth weight (g)	í148.8 (í297.0 to í0.5)	0.049*	í75.1 (í191.8 to 41.6)	0.207
Length (cm)	í0.183 (í0.912 to 0.546)	0.622	í0.140 (í0.712 to 0.432)	0.631
Chest circumference (cm)	í0.389 (í1.046 to 0.268)	0.245	í0.194 (í0.710 to 0.322)	0.460
Head circumference (cm)	í0.204 (í0.781 to 0.372)	0.486	í0.051 (í0.503 to 0.400)	0.823

Multiple regression model adjusted for maternal age, maternal educational level, smoking status during pregnancy, maternal BMI, parity, gestational age, and blood sampling period. For head circumference, adjusted model also includes delivery mode (cesarean section/vaginal). *; p < 0.05

女児



PFOS濃度が10倍になると（札幌コーホートの母体血中濃度は最低1.30ng/mL、最高16.2ng/mL）、女の子の出生体重が約270g小さくなる



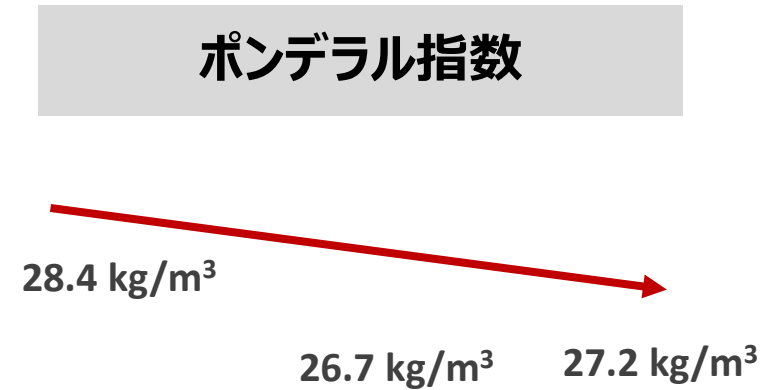
PFNA, PFDA濃度が高いと 出生体重が小さくなる (大規模コホート)

Prenatal exposure to 11 perfluoroalkyl substances and fetal growth: A large-scale, prospective birth cohort study

Ikuko Kashino^{a,b,c}, Seiko Sasaki^a, Emiko Okada^a, Hideyuki Matsuura^d, Houman Goudarzi^c, Chihiro Miyashita^c, Eisaku Okada^a, Yoichi M. Ito^c, Atsuko Araki^c, Reiko Kishi^{c,*}

胎児期曝露	出生体重 (n=1985)		出生身長 (n=1983)		出生児頭囲 (n=1976)	
	t	95% CI	t	95% CI	t	95% CI
log ₁₀ PFHxS (C6)	-3.0	(-60.5, 54.4)	0.028	(-0.284, 0.340)	-0.155	(-0.427, 0.117)
log ₁₀ PFOS (C8)	-35.0	(-109.0, 39.0)	0.092	(-0.311, 0.494)	-0.067	(-0.418, 0.283)
log ₁₀ PFOA (C8)	-18.7	(-69.8, 32.4)	-0.032	(-0.309, 0.246)	0.053	(-0.189, 0.295)
log ₁₀ PFNA (C9)	-96.2	(-165.3, -27.1)	-0.480	(-0.856, -0.105)	-0.297	(-0.625, 0.030)
log ₁₀ PFDA (C10)	-72.2	(-138.1, -6.3)	-0.133	(-0.491, 0.225)	-0.239	(-0.551, 0.072)
log ₁₀ PFUnDA (C11)	-62.5	(-125.4, 0.4)	-0.006	(-0.348, 0.336)	-0.204	(-0.502, 0.094)
log ₁₀ PFDoA (C12)	-57.1	(-122.5, 8.3)	-0.174	(-0.529, 0.182)	-0.264	(-0.573, 0.046)
log ₁₀ PFTTrDA (C13)	-42.2	(-108.8, 24.4)	0.168	(-0.194, 0.529)	-0.242	(-0.557, 0.073)

PFOS濃度が高いと、アディポネクチン値が高く、ポNDERAL指数が低い



PFOS濃度 低 高

低 高

* アディポネクチン：脂肪細胞から分泌されるタンパク質、セラミドの排出を促し、成人であればインスリンのはたらきを正常に戻す、動脈硬化を防ぐ、心臓を保護するなどの良い働きがある

** ポンデラル指数（胎児の肥満度指標） = 体重(kg)/身長(cm)³

PFOSのポンデラル指数低下は アディポネクチンを介したメカニズム ではないだろう

Adjusted for maternal pre pregnancy BMI, parity, maternal smoking during pregnancy, blood sampling period, gestational age, and infant sex

B C indicates total effects

* $p < 0.05$ and ** $P < 0.01$

- PFOS曝露は臍帯血中の総アディポネクチン濃度を増加させ、アディポネクチン濃度の増加は、ポンデラル指数（体格指数）を増加させている。
- しかしながら、直接的にはPFOS曝露はポンデラル指数を低下させている。
- つまり、PFOS曝露とポンデラル指数の低下の関係は、アディポネクチンを媒介したメカニズムではなく、他のルートで引き起こされていると推測される。

アウトライン

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③ 甲状腺ホルモン・発達

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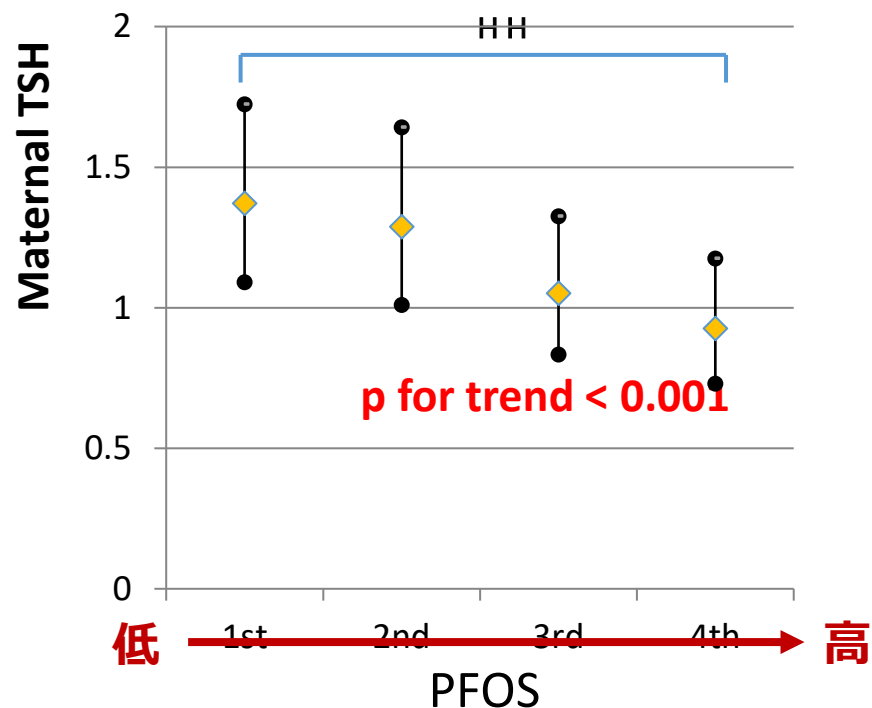
V. \è\Ò\ë\Õ û\²\Ð

Association of perfluorinated chemical exposure in utero with maternal and infant thyroid hormone levels in the Sapporo cohort of Hokkaido Study on the Environment and Children's Health

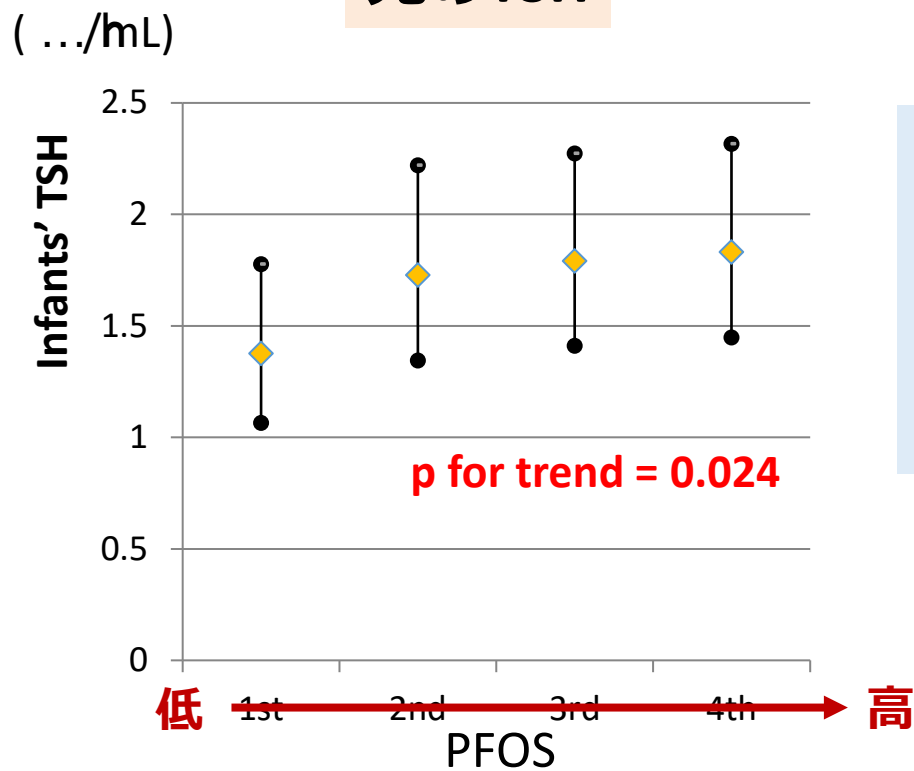
Shizue Kato¹ · Sachiko Itoh² · Motoyuki Yuasa³ · Toshiaki Baba¹ · Chihiro Miyashita² · Seiko Sasaki¹ · Sonomi Nakajima⁴ · Akiko Uno¹ · Hiroyuki Nakazawa⁵ · Yusuke Iwasaki⁵ · Emiko Okada¹ · Reiko Kishi²

母のPFOS濃度は母のTSHと逆相関、児のTSHとは正の相関 (札幌コーホート)

母のTSH



児のTSH



胎児期のPFOS曝露は視床下部-下垂体-甲状腺軸 (HPT軸) に影響する



Association between perfluoroalkyl substance exposure and thyroid hormone/thyroid antibody levels in maternal and cord blood: The Hokkaido Study



Sachiko Itoh^a, Atsuko Araki^a, Chihiro Miyashita^a, Keiko Yamazaki^a, Houman Goudarzi^{a,b}, Machiko Minatoya^{a,c}, Yu Ait Bama^a, Sumitaka Kobayashi^a, Emiko Okada^d, Ikuko Kashino^d, Motoyuki Yuasa^e, Toshiaki Baba^{a,f}, Reiko Kishi^{a,g}

母の甲状腺抗体無群では、 児の甲状腺ホルモンおよび 抗体値が低い（男児） （北海道コーホート）

	PFAS	母の甲状腺抗体なし群 (n=211)		母の甲状腺抗体あり群 (n=48)		p-interaction
		B (95% CI)	p-value	B (95% CI)	p-value	
TSH ^a	PFOS (C8)	0.389 (0.122, 0.656)	0.005	N.S.		N.S.
	PFDA (C10)	N.S.		-1.036 (-1.644, -0.428)	0.004	N.S.
FT3 ^a	PFDA (C10)	-0.186 (-0.366, -0.006)	0.043	N.S.		N.S.
	PFUnDA(C11)	-0.172 (-0.329, -0.014)	0.033	N.S.		N.S.
抗甲状腺抗体 ^b	PFOA (C8)	-0.134 (-0.266, -0.002)	0.047	N.S.		N.S.
	PFTTrDA (C13)	-0.119 (-0.226, -0.013)	0.028	N.S.		0.008

^aAdjusted for maternal factors (age at delivery, parity, M* \bar{n} T, alcohol consumption, smoking during pregnancy, pre-pregnancy BMI, logFT4).

^bAdjusted for maternal factors (age at delivery, parity, M* \bar{n} T, alcohol consumption, smoking during pregnancy, pre-pregnancy BMI).

“N.S.” means not significant association.

- 〈 PFOS値が高いとTSH値が高いことは H]]d]C]d]0\Ø e Y\Ø ³ ±
- 〈 母の抗甲状腺抗体が、PFOSによる胎児のTH分泌かく乱への脆弱性から守っている可能性を示唆

母の甲状腺抗体の有無で層別した、胎児期PFAS曝露が 児の甲状腺ホルモンとの関連（女兒）（北海道コホート）

PFAS	母の甲状腺抗体なし群 (n=195)		母の甲状腺抗体あり群 (n=45)		p-interaction
	B (95% CI)	p-value	B (95% CI)	p-value	
TSH ^a	PFDoDA(C12)	-0.181 (-0.345, -0.018)	0.030	N.S.	N.S.
FT3 ^a	PFDA (C10)	0.258 (0.057, 0.460)	0.013	N.S.	N.S.
	PFTTrDA (C13)	0.226 (0.070, 0.382)	0.005	N.S.	0.031
FT4 ^a	PFDoDA(C12)	N.S.		-0.077 (-0.148, -0.006)	0.037
抗甲状腺抗体 ^b	PFOA (C8)	N.S.		0.266 (0.095, 0.437)	0.007
	PFNA (C9)	N.S.		0.284 (0.070, 0.498)	0.015
	PFDA (C10)	N.S.		0.267 (0.145, 0.389)	<0.001
	Total PFAS	N.S.		0.495 (0.205, 0.786)	0.004

- 母の甲状腺抗体の無群では、胎児期PFAS曝露が児のT3値と正の相関
- 母の甲状腺抗体の有群（甲状腺疾患のリスクが高い）で抗甲状腺抗体が高くなることから、女性で甲状腺機能と関係する自己免疫疾患が多いことを支持する結果



PFOAはベイリー乳幼児発達検査による、女児の認知発達を遅らせるかもしれない (札幌コーホート)



Prenatal exposure to perfluorinated chemicals and neurodevelopment in early infancy: The Hokkaido Study

Houman Goudarzi^a, Sonomi Nakajima^b, Tamiko Ikeno^a, Seiko Sasaki^c, Sachiko Kobayashi^a, Chihiro Miyashita^a, Sachiko Ito^a, Atsuko Araki^a, Hiroyuki Nakazawa^d, Reiko Kishi^{a,*}

		1 月 (n=14)	4 月 (n=14)
6 ヶ月時	PFOS	0.02 (-4.52, 5.59)	0.04 (-6.38, 10.37)
	PFOA	-0.05 (-4.33, 2.56)	-0.01 (-5.93, 5.50)
	PFOA-# \hat{e} $\hat{\epsilon}$	0.11 (-3.31, 7.41)	0.07 (-5.56, 9.26)
	PFOA-\hat{e} $\hat{\epsilon}$	-0.30 (-11.96, -0.68)*	0.06 (-8.37, 12.93)
18 ヶ月時	PFOS-all	0.05 (-9.91, 16.66)	-0.02 (-13.45, 10.72)
	PFOA-all	-0.08 (-11.74, 5.28)	0.00 (-7.66, 7.85)

Adjusted for gestational age, parity, maternal age, smoking and alcohol consumption during pregnancy, G9 GcG5G2Gc, G9 GcG5G2Gc, maternal education, blood sampling period, breast feeding, and total dioxin levels (TEQ, WHO 2005).
* p < 0.05.

The association between prenatal perfluoroalkyl substance exposure and symptoms of attention-deficit/hyperactivity disorder in 8-year-old children and the mediating role of thyroid hormones in the Hokkaido study

Sachiko Itoh^a, Keiko Yamazaki^a, Satoshi Suyama^b, Atsuko Ikeda-Araki^{a,c}, Chihiro Miyashita^a, Yu Ait Bamai^a, Sumitaka Kobayashi^a, Hideyuki Masuda^a, Takeshi Yamaguchi^a, Houman Goudarzi^{a,d}, Emiko Okada^e, Ikuko Kashino^a, Takuya Saito^b, Reiko Kishi^{a,*}

PFASは8歳児のADHD リスクをむしろ下げる (北海道コーホート)

Table 5
 Adjusted odds ratios for an increase of maternal PFAS levels on ADHD symptom (Total scores, Inattention, Hyperactivity-impulsivity) according to the birth order.

	All children ^a			Boys ^b			Girls ^b								
	First-born		Second or later	First-born		Second or later	First-born		Second or later	p-int					
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)							
Total scores															
PFHxS (C6)	0.63	(0.38, 1.03)	0.76	(0.42, 1.36)	0.681	0.74	(0.37, 1.48)	0.88	(0.37, 2.10)	0.901	0.57	(0.27, 1.23)	0.64	(0.29, 1.42)	0.514
PFOS (C8)	0.48	(0.22, 1.04)	1.54	(0.68, 3.48)	0.208	0.55	(0.18, 1.69)	1.55	(0.49, 4.92)	0.315	0.43	(0.14, 1.33)	1.41	(0.44, 4.50)	0.509
PFOA (C8)	0.75	(0.44, 1.29)	1.60	(0.85, 3.02)	0.101	0.91	(0.46, 1.78)	5.18	(1.63, 16.51)*	0.011	0.61	(0.24, 1.57)	0.87	(0.39, 1.91)	0.603
PFNA (C9)	0.71	(0.38, 1.32)	0.78	(0.37, 1.66)	0.945	0.48	(0.18, 1.28)	0.49	(0.15, 1.64)	0.777	0.99	(0.41, 2.35)	1.05	(0.38, 2.92)	0.730
PFDA (C10)	0.64	(0.35, 1.15)	0.82	(0.39, 1.69)	0.631	0.61	(0.27, 1.38)	0.51	(0.18, 1.49)	0.779	0.67	(0.26, 1.75)	1.15	(0.41, 3.21)	0.473
PFUnDA(C11)	0.68	(0.45, 1.04)	1.13	(0.67, 1.92)	0.301	0.79	(0.44, 1.42)	0.87	(0.42, 1.81)	0.973	0.54	(0.28, 1.06)	1.47	(0.67, 3.23)	0.164
PFDoDA(C12)	0.73	(0.43, 1.24)	0.97	(0.55, 1.73)	0.656	0.62	(0.30, 1.30)	1.25	(0.51, 3.05)	0.229	0.87	(0.38, 1.96)	0.80	(0.38, 1.71)	0.603
PFTriDA (C13)	0.57	(0.36, 0.91)*	1.55	(0.81, 2.96)	0.088	0.74	(0.39, 1.40)	1.42	(0.53, 3.83)	0.532	0.46	(0.23, 0.95)*	1.57	(0.65, 3.78)	0.107
Total PFAS (nmol/mL)	0.45	(0.19, 1.05)	1.42	(0.53, 3.82)	0.185	0.55	(0.17, 1.78)	2.35	(0.49, 11.17)	0.217	0.36	(0.09, 1.40)	0.94	(0.25, 3.54)	0.567
Inattention															
PFHxS (C6)	0.65	(0.39, 1.09)	0.80	(0.44, 1.44)	0.948	1.08	(0.52, 2.25)	1.11	(0.45, 2.72)	0.379	0.37	(0.17, 0.84)*	0.59	(0.26, 1.33)	0.244
PFOS (C8)	0.56	(0.26, 1.23)	1.85	(0.81, 4.23)	0.345	1.24	(0.40, 3.86)	3.16	(0.97, 10.26)	0.702	0.26	(0.08, 0.87)*	1.00	(0.31, 3.24)	0.509
PFOA (C8)	0.82	(0.47, 1.43)	1.14	(0.61, 2.15)	0.597	0.99	(0.48, 2.00)	3.29	(1.11, 9.71)*	0.107	0.65	(0.25, 1.67)	0.62	(0.27, 1.40)	0.864
PFNA (C9)	0.79	(0.42, 1.46)	0.73	(0.35, 1.54)	0.657	0.75	(0.28, 2.00)	0.55	(0.18, 1.74)	0.691	0.83	(0.35, 1.98)	0.88	(0.32, 2.44)	0.701
PFDA (C10)	0.77	(0.42, 1.40)	0.84	(0.41, 1.73)	0.907	0.88	(0.39, 2.02)	0.73	(0.23, 2.06)	0.702	0.65	(0.25, 1.71)	0.93	(0.33, 2.63)	0.621
PFUnDA(C11)	0.68	(0.45, 1.02)	1.08	(0.73, 1.59)	0.421	0.83	(0.48, 1.42)	1.03	(0.59, 1.78)	0.727	0.47	(0.22, 1.01)	1.14	(0.65, 2.01)	0.130
PFDoDA(C12)	0.67	(0.39, 1.15)	0.87	(0.49, 1.54)	0.888	0.50	(0.23, 1.06)	1.46	(0.60, 3.58)	0.278	0.91	(0.40, 2.07)	0.58	(0.27, 1.26)	0.223
PFTriDA (C13)	0.56	(0.35, 0.90)*	1.58	(0.82, 3.03)	0.090	0.62	(0.32, 1.18)	1.57	(0.60, 4.11)	0.360	0.54	(0.27, 1.11)	1.55	(0.63, 3.81)	0.188
Total PFAS (nmol/mL)	0.54	(0.23, 1.28)	1.22	(0.46, 3.24)	0.502	1.09	(0.33, 3.60)	2.90	(0.68, 12.37)	0.605	0.22	(0.05, 0.94)*	0.55	(0.14, 2.15)	0.704
Hyperactivity-impulsivity															
PFHxS (C6)	0.63	(0.39, 0.99)*	0.94	(0.56, 1.59)	0.217	0.53	(0.28, 1.02)	0.77	(0.35, 1.68)	0.682	0.77	(0.39, 1.59)	1.19	(0.58, 2.42)	0.185
PFOS (C8)	0.38	(0.18, 0.81)*	1.21	(0.59, 2.48)	0.074	0.45	(0.16, 1.30)	1.00	(0.35, 2.83)	0.510	0.31	(0.11, 0.93)*	1.79	(0.59, 5.38)	0.062
PFOA (C8)	0.76	(0.45, 1.26)	1.41	(0.82, 2.45)	0.085	0.79	(0.41, 1.52)	1.86	(0.70, 4.90)	0.177	0.74	(0.31, 1.75)	1.29	(0.65, 2.58)	0.256
PFNA (C9)	0.59	(0.32, 1.07)	1.01	(0.52, 1.94)	0.189	0.32	(0.12, 0.83)*	0.80	(0.28, 2.32)	0.164	0.93	(0.42, 2.09)	1.14	(0.52, 2.94)	0.727
PFDA (C10)	0.65	(0.37, 1.14)	1.17	(0.60, 2.25)	0.144	0.67	(0.31, 1.44)	1.14	(0.41, 3.18)	0.430	0.60	(0.25, 1.46)	1.16	(0.48, 2.85)	0.241
PFUnDA(C11)	0.62	(0.42, 0.93)*	1.20	(0.76, 1.91)	0.054	0.66	(0.38, 1.15)	1.55	(0.70, 3.44)	0.128	0.55	(0.29, 1.05)	1.03	(0.56, 1.88)	0.177
PFDoDA(C12)	0.60	(0.36, 0.99)*	1.14	(0.69, 1.90)	0.049	0.45	(0.22, 0.92)*	1.81	(0.77, 4.26)	0.016	0.83	(0.39, 1.77)	0.90	(0.46, 1.76)	0.693
PFTriDA (C13)	0.59	(0.37, 0.92)*	1.54	(0.89, 2.66)	0.010	0.60	(0.32, 1.10)	2.93	(1.06, 8.08)*	0.037	0.60	(0.30, 1.17)	1.20	(0.61, 2.36)	0.094
Total PFAS (nmol/mL)	0.36	(0.16, 0.82)*	1.44	(0.61, 3.40)	0.031	0.37	(0.12, 1.14)	1.57	(0.41, 6.08)	0.191	0.33	(0.09, 1.19)	1.69	(0.50, 5.74)	0.087

a: Adjusted for maternal factors (age at delivery, parity, educational level, pre-pregnancy BMI, alcohol intake during pregnancy, smoking habit during pregnancy) and children's sex.
 b: Adjusted for maternal factors (age at delivery, parity, educational level, pre-pregnancy BMI, alcohol intake during pregnancy and smoking habit during pregnancy).
 p-int shows the p-interaction between two groups "first-born" and "second or later".
 PFAS: perfluoroalkyl substance, PFHxS: perfluorohexane sulfonate, PFOS: perfluorooctane sulfonate, PFOA: perfluorooctanoate, PFNA: perfluorononanoic acid, PFDA: perfluorodecanoic acid, PFUnDA: perfluoroundecanoic acid, PFDoDA: perfluorododecanoic acid, PFTriDA: perfluorotridecanoic acid.
 *represented p value < 0.05.

- メカニズムとして甲状腺ホルモンの介在を仮説としたが、認められた関連はわずかだった (PFUnDA曝露とFT4のみ)
- PFASはWWZへのアゴニストであり、神経保護作用がある(Power et al. 2013; Stein et al. 2013)ため?
- 免疫抑制のため(Liew et al., 2018)?

アウトライン

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④ 性ホルモン・ステロイドホルモン

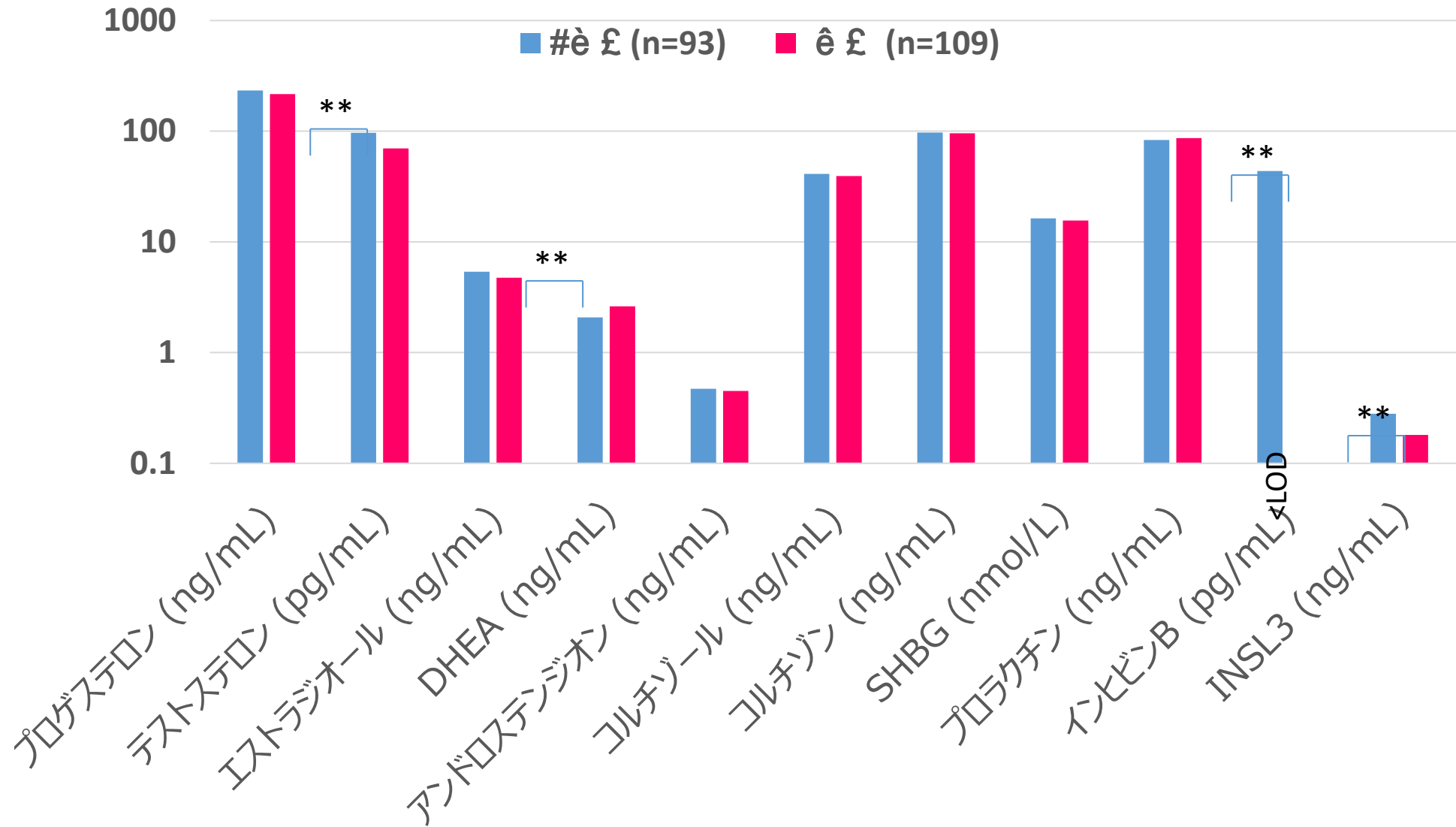
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出生時の性ホルモン値（臍帯血中）



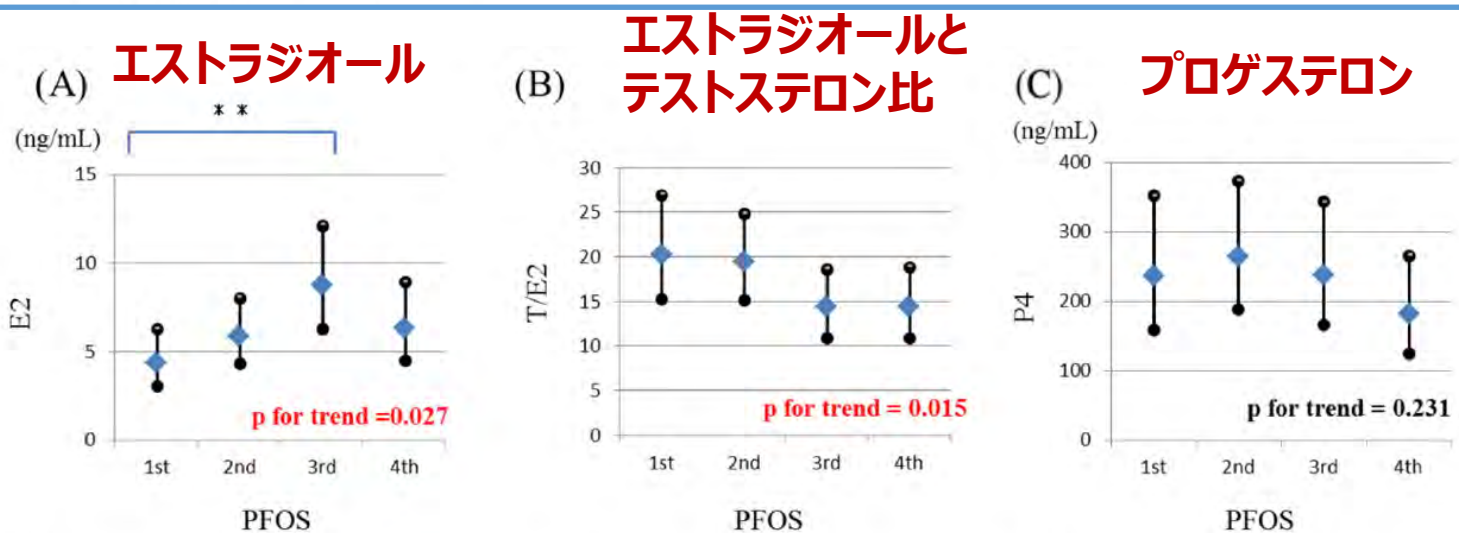
Bar shows the median concentration of each hormone. Mann-Whitney U-test **p<0.01. INSL3 were measured for 20 samples for girls.



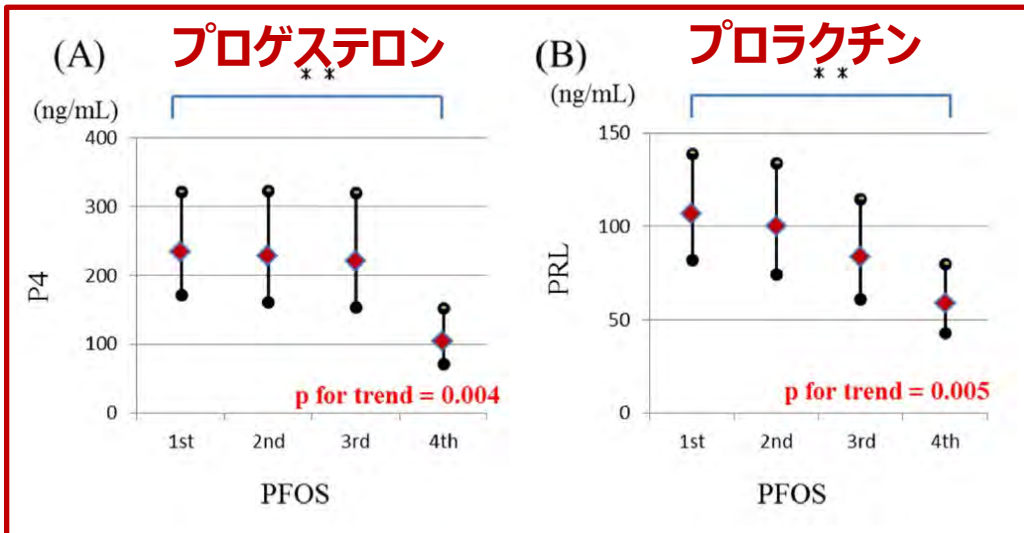
Association of perfluoroalkyl substances exposure in utero with reproductive hormone levels in cord blood in the Hokkaido Study on Environment and Children's Health

Sachiko Itoh ^a, Atsuko Araki ^a, Takahiko Mitsui ^b, Chihiro Miyashita ^a, Houman Goudarzi ^a, Seiko Sasaki ^c, Kazutoshi Cho ^d, Hiroyuki Nakazawa ^e, Yusuke Iwasaki ^e, Nobuo Shinohara ^f, Katsuya Nonomura ^{f,g}, Reiko Kishi ^{a,*}

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d- B Ë Ó\Ö 男児\Ø エストラジオール値を上げる、テストステロンエスト
ラジオール比を下げる\•è\É 女児\Ñ
プロゲステロンとプロラクチン値を有
意に下\¼\É\ž
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男児



女児

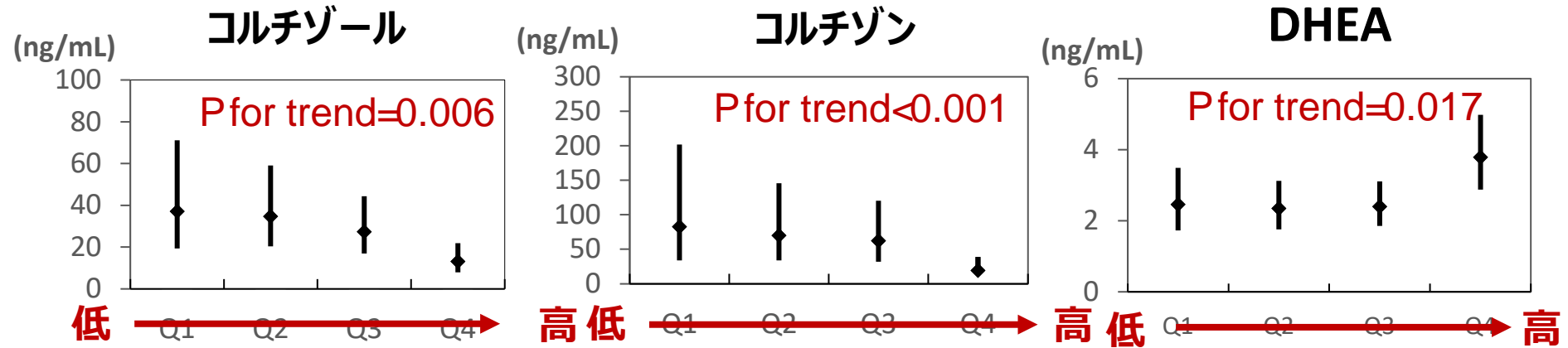
The Association of Prenatal Exposure to Perfluorinated Chemicals with Glucocorticoid and Androgenic Hormones in Cord Blood Samples: The Hokkaido Study

Houman Goudarzi,¹ Atsuko Araki,¹ Sachiko Itoh,¹ Seiko Sasaki,² Chihiro Miyashita,¹ Takahiko Mitsui,³ Hiroyuki Nakazawa,⁴ Katsuya Nonomura,^{5,6} and Reiko Kishi¹

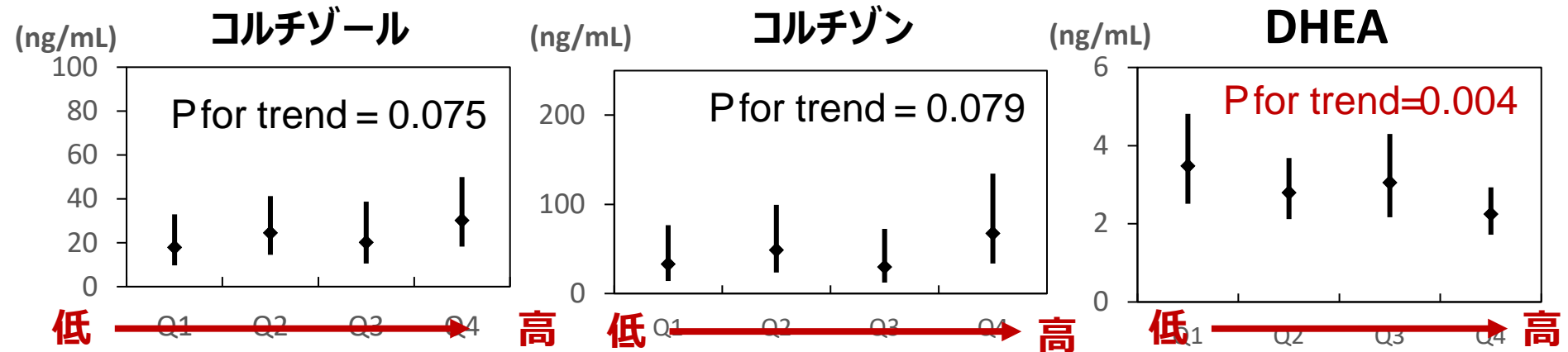
¹Center for Environmental and Health Sciences, Hokkaido University, Sapporo, Japan; ²Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo, Japan; ³Department of Urology, Hokkaido University Hospital, Sapporo, Hokkaido, Japan; ⁴Department of Analytical Chemistry, Faculty of Pharmaceutical Sciences, Hoshi University, Tokyo, Japan; ⁵Department of Renal and Genitourinary Surgery, Graduate School of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan; ⁶Kushiro Rosai Hospital, Kushiro, Japan

胎児期のPFOS曝露は糖質コルチコイドと負の相関、副腎アンドロゲンと正の相関

PFOS

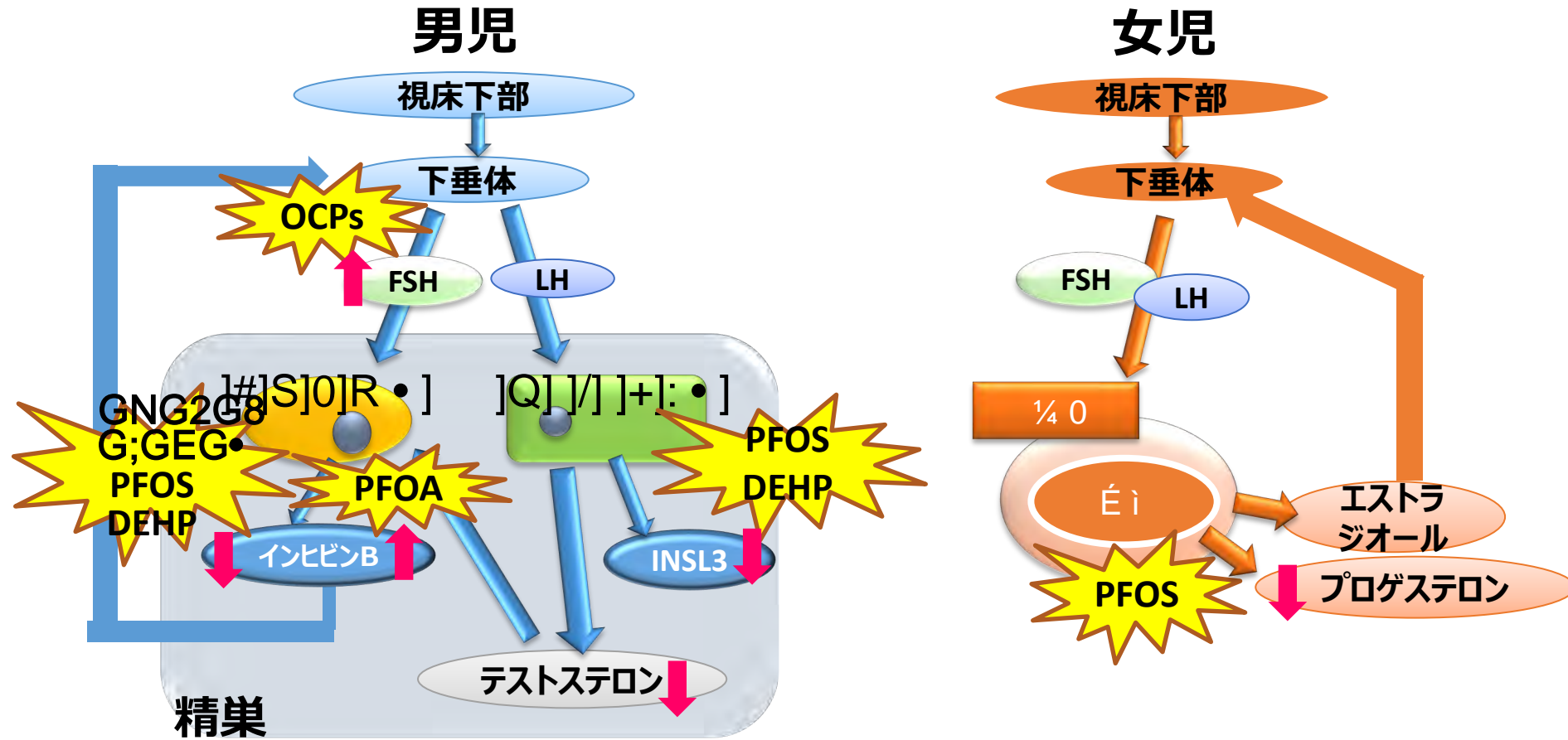


PFOA



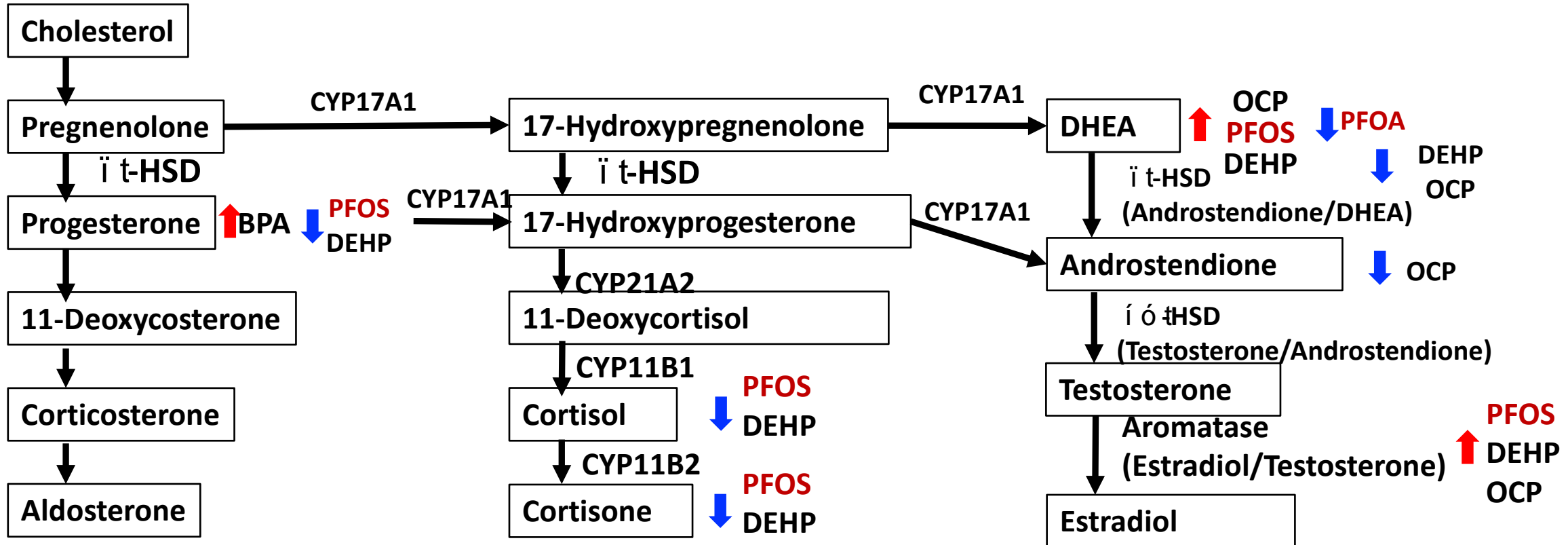
Adjusted for gestational age, maternal age, smoking and G9GcG5G2Gc during pregnancy, parity, maternal M*ñ T and the blood sampling period. Q: quartile

出生時の視床下部－下垂体－性腺軸のかく乱の可能性



Araki et al., 2014, 2016, 2018; Itoh et al., 2016;
Goudarzi et al., 2017, Minatoya et al., 2017; Miyashita et al., 2018

出生時のステロイドホルモン代謝系のかく乱の可能性



アウトライン

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⑤ 免疫・アレルギー

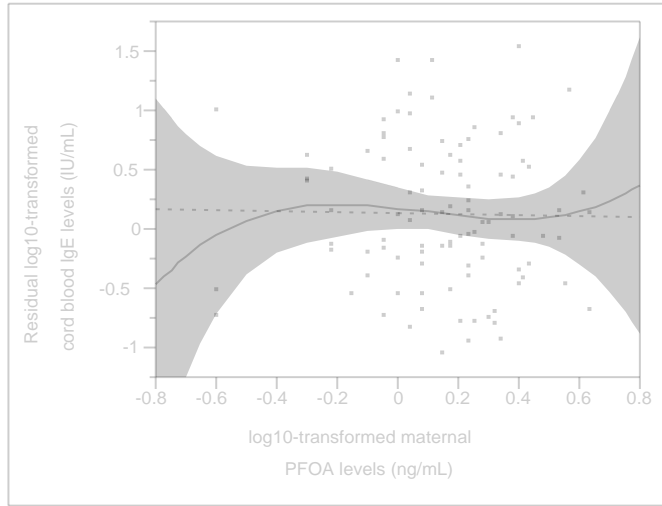
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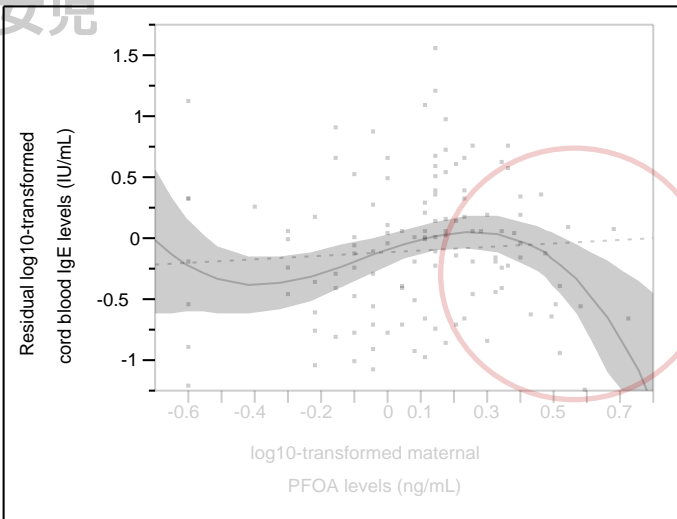
V. \è\Ò\ë\Õ û\²\Ð

出生時のIgE(臍帯血)

男児



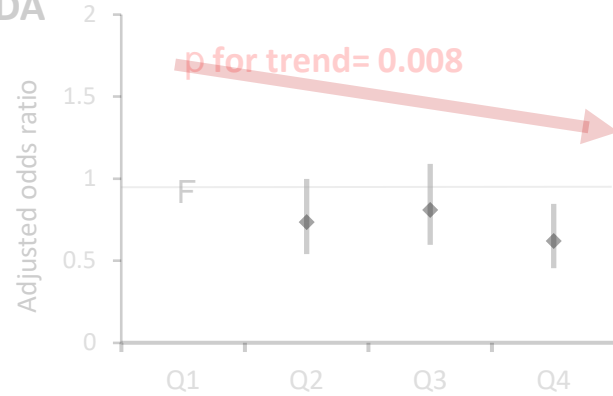
女児



4歳児のアレルギー・感染症罹患歴

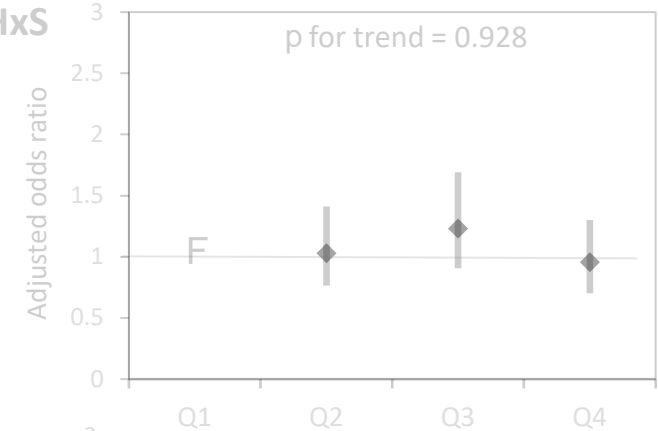
アレルギー

PFDODA



感染症罹患歴

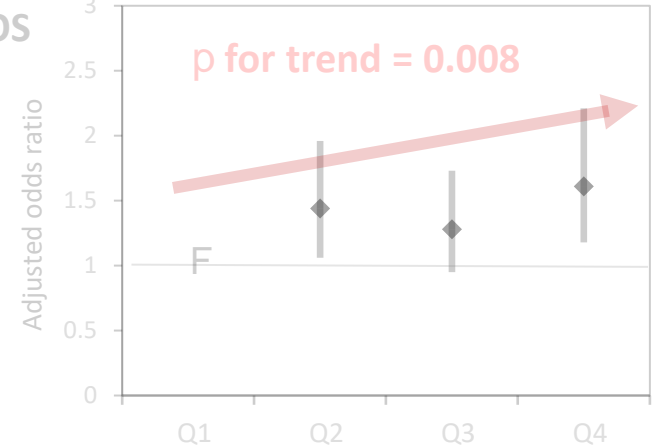
PFHxS



PFTrDA



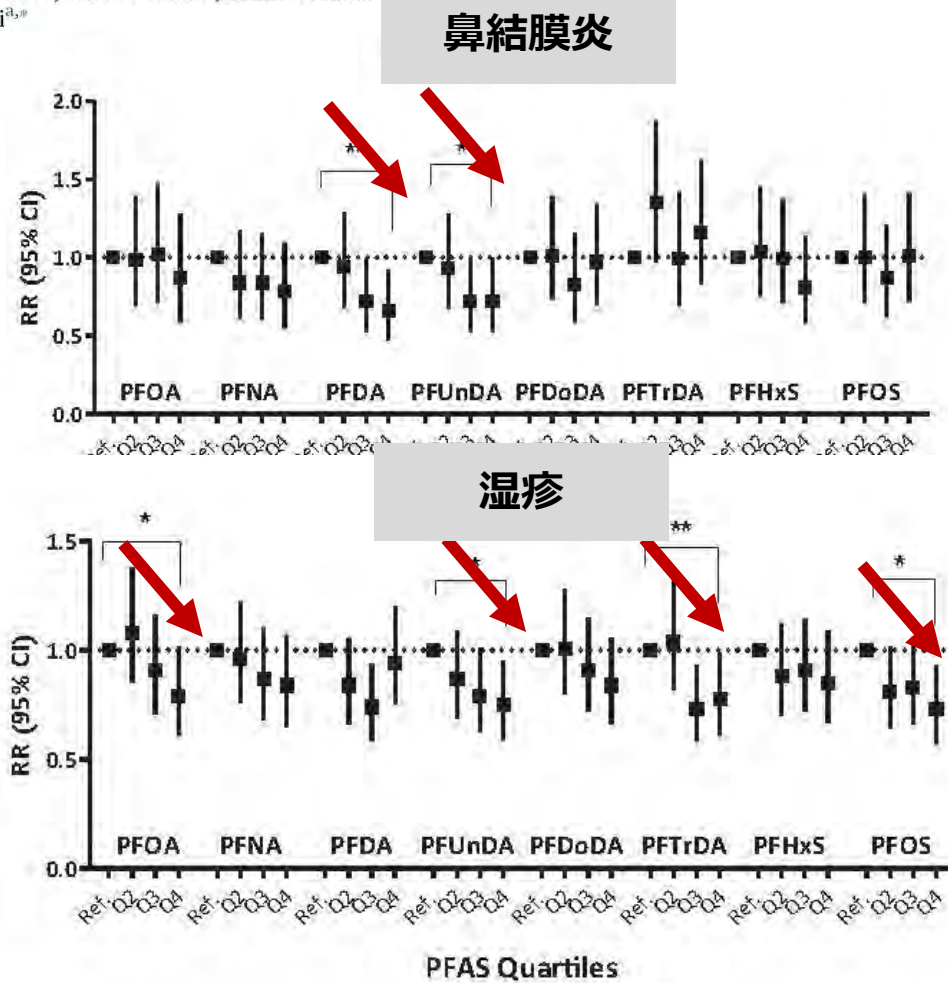
PFOS





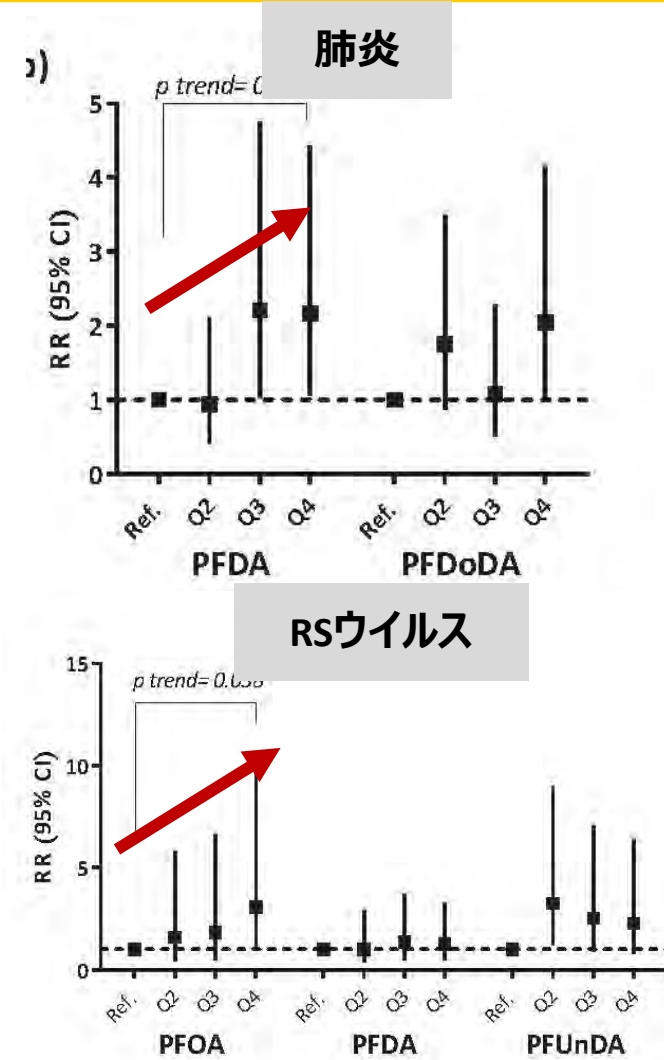
Effect of prenatal exposure to per- and polyfluoroalkyl substances on childhood allergies and common infectious diseases in children up to age 7 years: The Hokkaido study on environment and children's health

Yu Ait Bamai^a, Houman Goudarzi^{a,b}, Atsuko Araki^a, Emiko Okada^{a,c}, Naoko Yoshida^a, Chihiro Miyashita^a, Reiko Kishi^{a,*}



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• **次世代の免疫毒性の** í š \ü , ®\ž



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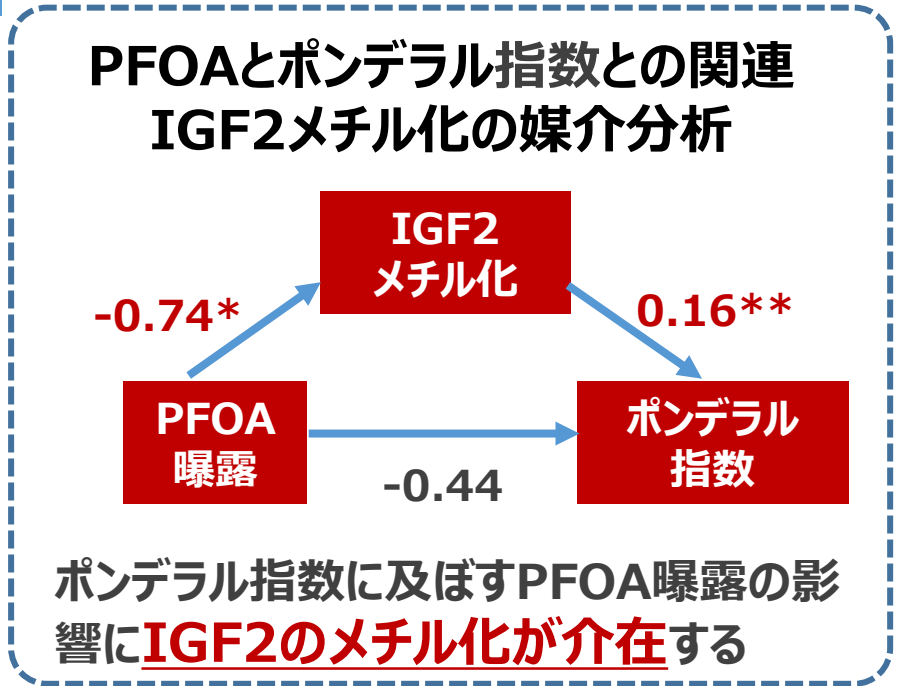
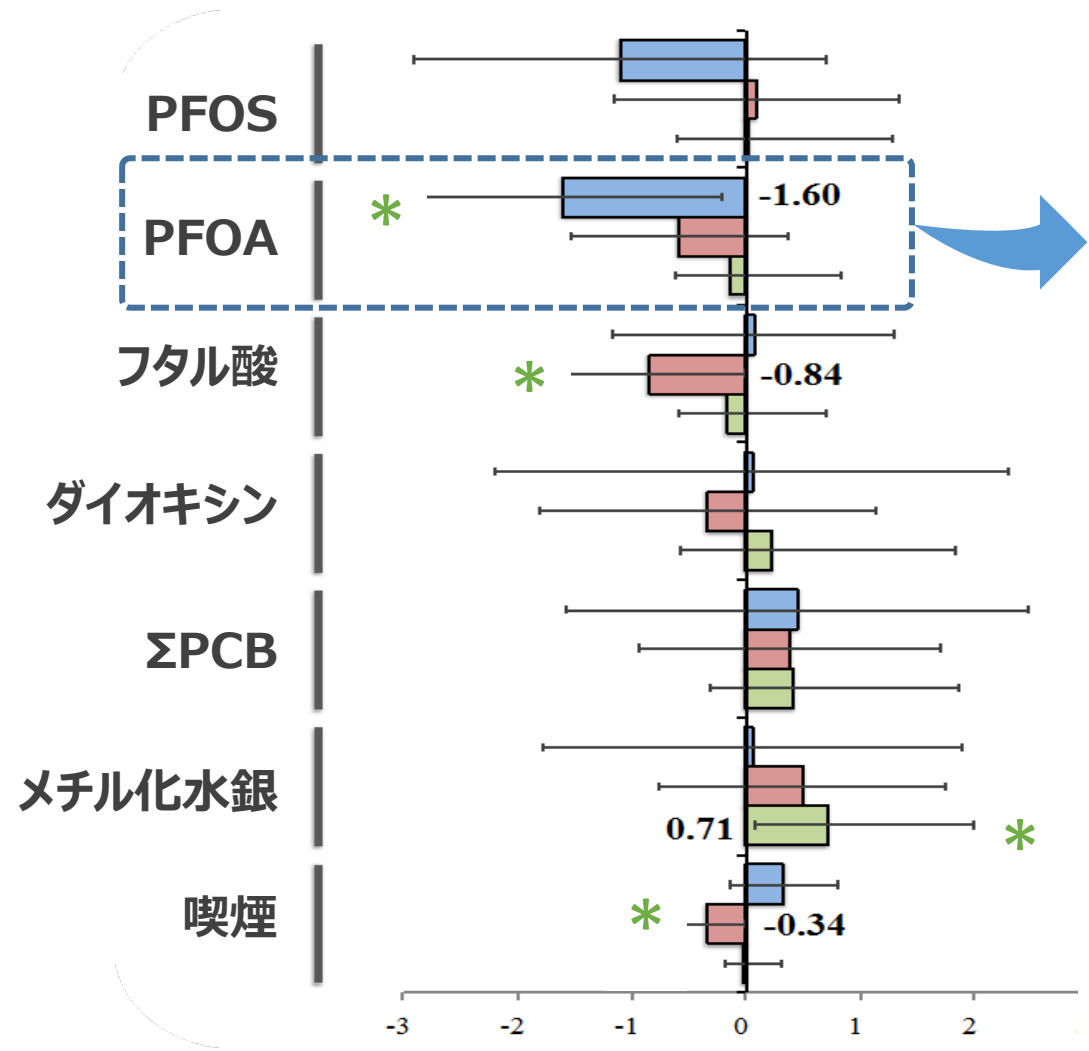
⑥ エピゲノム (DNAメチル化)

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V. \è\Ò\ë\Õ û\²\Ð

メカニズムのひとつとしてエピゲノム変化が介在する可能性を示唆

環境化学物質曝露と遺伝子DNAメチル化



出生コーホートにおいてエピゲノム変化を観察する必要性を示唆

■ IGF2 $\uparrow \hat{\gamma} \hat{\delta} \ll \tilde{O}$
 yH19 $\uparrow \hat{\gamma} \hat{\delta} \ll \tilde{O}$
 yLINE1 Global methylation

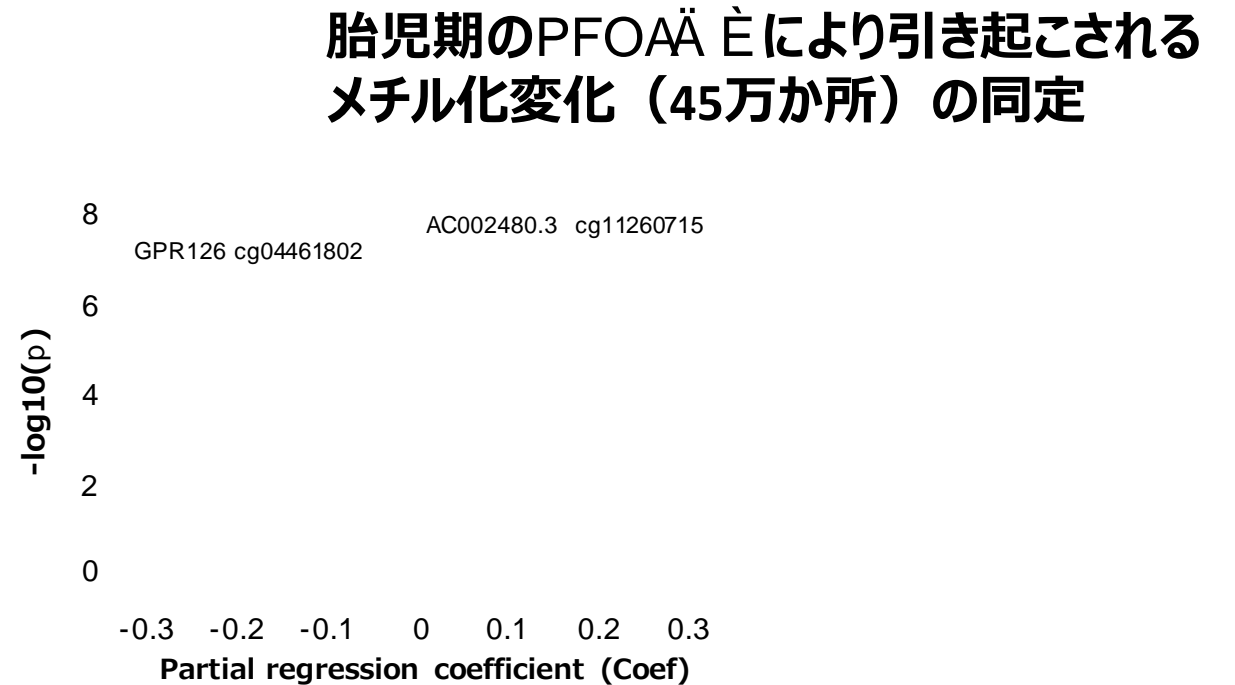


PFOS、PFOA曝露と臍帯血中のDNAメチル化変化

An epigenome-wide study of cord blood DNA methylations in relation to prenatal perfluoroalkyl substance exposure: The Hokkaido study



Ryu Miura^a, Atsuko Araki^a, Chihiro Miyashita^a, Sumitaka Kobayashi^a, Sachiko Kobayashi^a, Shu-Li Wang^b, Chung-Hsing Chen^{c,d}, Kunio Miyake^e, Mayumi Ishizuka^f, Yusuke Iwasaki^g, Yoichi M. Ito^h, Takeo Kubotaⁱ, Reiko Kishi^{a,*}



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 CYP2E1 } \½\ö\ó\Ø) « Õ\Ø]I])S ò\Ù]R]M]]F]Y\Ø Ý ô (Mok et al. 2017)
 DUSP22
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(Riso et al. 2016)
 (Kresovich et al. 2017)

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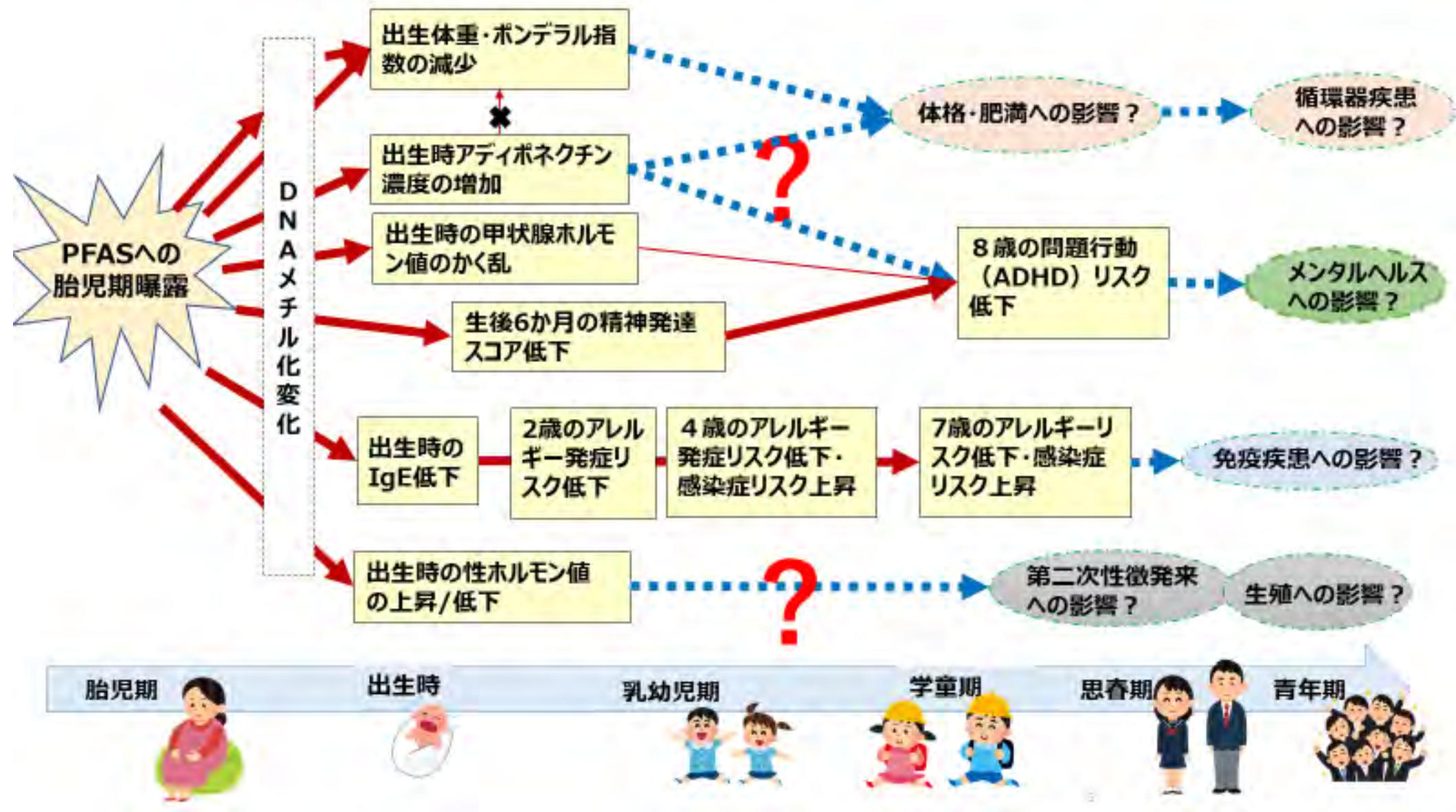
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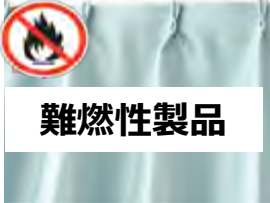





IV. 今後の研究課題と方向性

V. \è\Ò\ë\Õ\μ\²\Ð

残された課題 1 : 関連の意味は？ 影響はいつまで続くのか？



残された課題 2 : 様々な化学物質への曝露

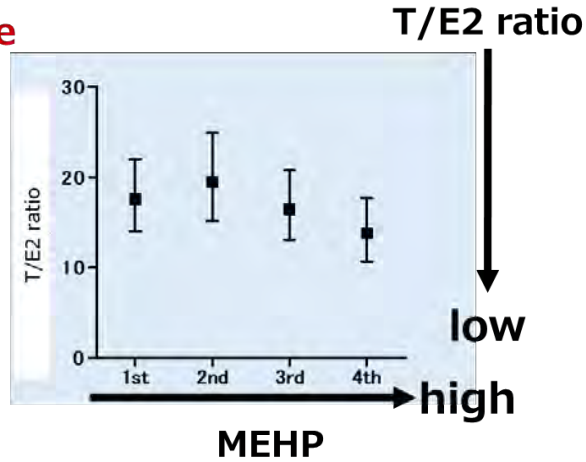
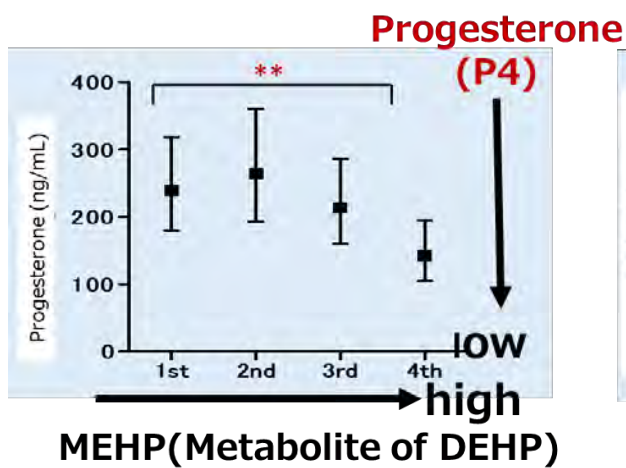
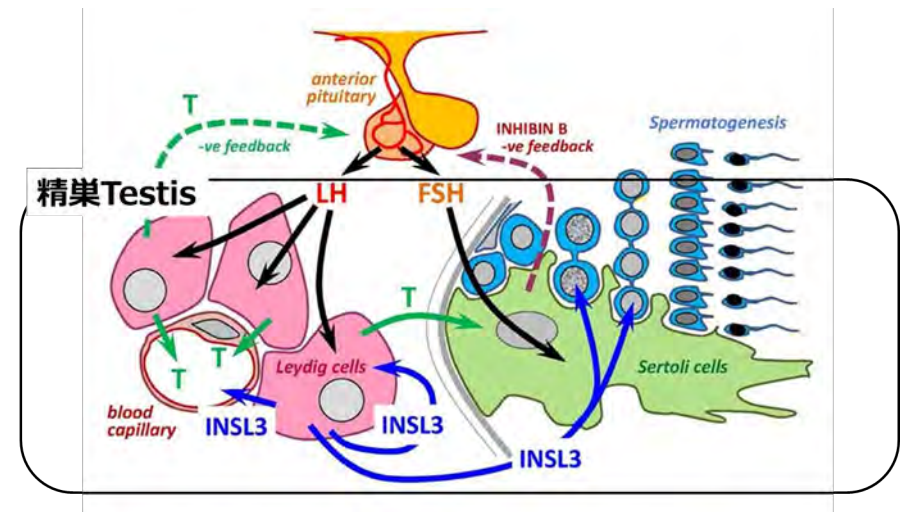
有機フッ素化合物 (PFAS)	リン酸トリエステル類 (PFR)	フタル酸エステル類 (PE)	ビスフェノール類 (BP)
撥水・発油剤、コーティング剤	可塑性難燃剤・ホリウレタンフォーム	PVC・プラスチックの可塑剤	樹脂硬化剤、コーティング剤
 <p>食事</p>  <p>飲料水</p>  <p>テフロン製品</p>  <p>撥水製品</p>	 <p>難燃性製品</p>  <p>ホリウレタンフォーム</p>  <p>電化製品</p>  <p>床材・ワックス</p>	 <p>プラスチック製容器</p>  <p>PVC 製品</p> <p>シャンプー、化粧品 ボディケア製品</p>	 <p>缶食品</p>  <p>ポリカーボネート製品</p>



- 規制は**限定的**であり、**様々な類縁化合物や代替物質が製造**されている
- 食事、日用品の使用やハウスダストを介し、**恒常的に曝露**する

Association between Maternal Exposure to di(2-ethylhexyl) Phthalate and Reproductive Hormone Levels in Fetal Blood: The Hokkaido Study on Environment and Children's Health

Atsuko Araki¹, Takahiko Mitsui², Chihiro Miyashita¹, Tamie Nakajima³, Hisao Naito³, Sachiko Ito¹, Seiko Sasaki⁴, Kazutoshi Cho⁵, Tamiko Ikeno¹, Katsuya Nonomura⁶, Reiko Kishi^{1*}



p for trend=0.002

p for trend=0.101

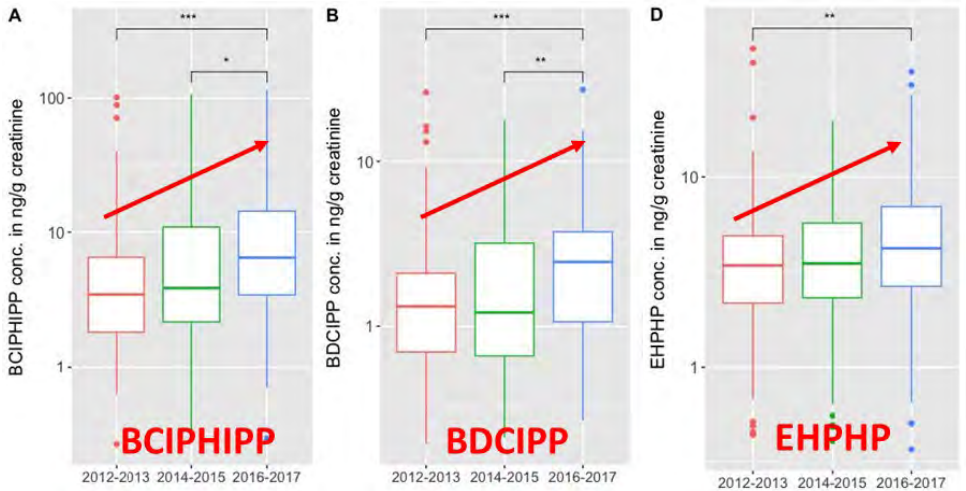
- 男児の血液中のテストステロン、Inhibin B、INSL-3濃度は、DEHP曝露量との負の相関を示した。
- 1歳児の血液中のテストステロン、Inhibin B、INSL-3濃度は、DEHP曝露量との負の相関を示した。

残された課題 3 : 子ども本人の曝露



Temporal trends and determinants of PFR exposure in the Hokkaido Study

Michiel Bastiaensen^{a,c}, Yu Ait Bamai^b, Atsuko Araki^d, Houman Goudarzi^{c,d}, Satoshi Konno^d, Sachiko Ito^b, Chihiro Miyashita^b, Yiming Yao^{a,c}, Reiko Kishi^b, Adrian Covaci^{a,c,e}



Secular trends of urinary phthalate metabolites in 7-year old children and association with building characteristics: Hokkaido study on environment and children's health

Rahel Mesfin Ketema^{a,b}, Yu Ait Bamai^{a,c}, Atsuko Ikeda-Araki^{a,b}, Takeshi Saito^b, Reiko Kishi^a

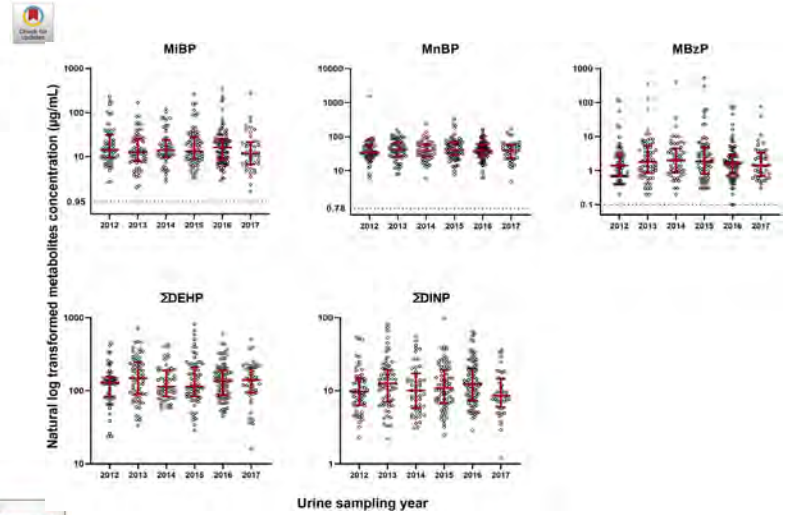
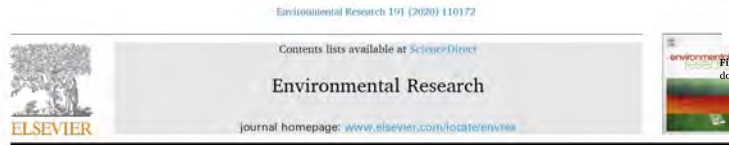
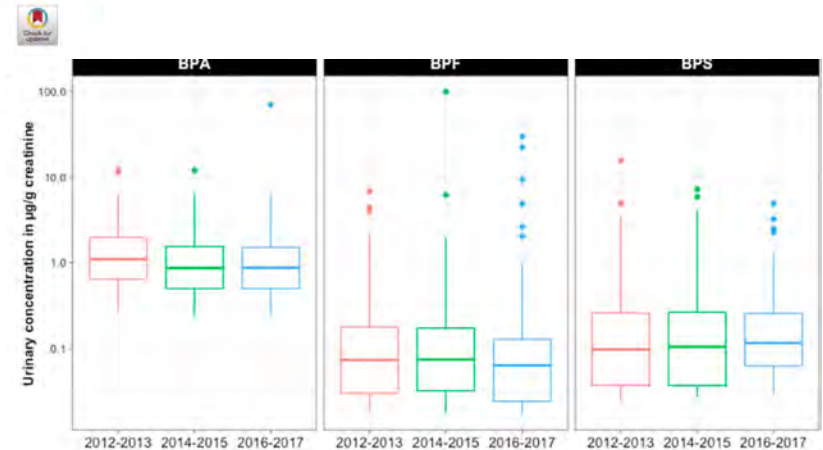


Fig. 1. Natural log transformed creatinine corrected concentration level of urinary phthalate metabolites. Bars represent interquartile ranges and median. Points on dotted line indicates samples with concentration limit of detection (<LOD).



Biomonitoring and temporal trends of bisphenols exposure in Japanese school children

Celine Gys^{a,c}, Yu Ait Bamai^b, Atsuko Araki^b, Michiel Bastiaensen^a, Noelia Caballero-Casero^a, Reiko Kishi^b, Adrian Covaci^a



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今後の方向性

- 出生コーホートの長期追跡：生殖やいわゆる生活習慣病への影響が検証できるのはこれから
- 何が曝露源になっているのか？

学童対面調査 (9-11y)

- 1) 2) 3) 4) 5) 6) 7) 8) 9) 10) 11) 12) 13) 14) 15) 16) 17) 18) 19) 20)
- 21) 22) 23) 24) 25) 26) 27) 28) 29) 30)
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思春期対面調査 (14-17y)

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今この辺
子ども本人の同意

生殖、非感染性疾患（糖尿病、脂質異常症、高血圧）、がん、他

研究から政策へ

規制（国レベル、国際レベル）

→ PFOS, PFOA, PFHxS
BPOPs
A/B 1/4
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表示

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WHO Collaborating Centre for Environmental Health and Prevention of Chemical Hazards

(WHO環境化学物質と健康障害予防研究協力センター)

2019 «4 ¾22 ©\Õ — s' B2 i C

活動

1. 化学物質の危険性に関する科学的知見の提供
2. 化学物質の危険性と健康影響に関するWHO資料の更新やまとめ
3. 化学物質の危険性と健康影響に関する知識の向上、研修や人材育成

<https://www.cehs.hokudai.ac.jp/whocc>



HEALTH IN THE SDG ERA



健康な環境と健康な人々は表裏一体(UNEP)

まとめにかえて (take-home message)

北海道スタディでは、有機フッ素化合物は低濃度であっても、胎児期曝露は次世代（生まれてくる赤ちゃん）に様々な健康影響がある可能性を示した

個人でできる対策（*私見）

- ① 可能な範囲でフッ素加工製品の使用頻度を減らす
- ② 電子レンジを使うときは、ガラスや陶器製品を用いる
- ③ 不必要な防汚加工、撥水加工製品は使わない
（特に子どもに使うもの）

ご清聴どうもありがとうございました!!

北海道スタディ参加者の皆さまに御礼申し上げます。

共同研究者・事務スタッフ



PFOA-frei gemäß EU VO
1907/2006 (geändert
durch 2017/1000)
*PFOA-free according to EU
regulation 1907/2006
(changed by 2017/1000)*



北海道スタディは、厚生労働科学研究費、環境省環境研究総合推進費、総務省、AMED、文部科学省科学研究費の助成によって実施しています。