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The association between prenatal per-and polyfluoroalkyl substance levels and Kawasaki disease among children of up to 4 years of age: A prospective birth cohort of the Japan Environment and Children's study

Hiroyoshi Iwata [a], Sumitaka Kobayashi [a,b], Mariko Itoh [a], Sachiko Itoh [a], Rahel Mesfin Ketema [a,c], Naomi Tamura [a], Chihiro Miyashita [a], Takeshi Yamaguchi [a], Keiko Yamazaki [a], Hideyuki Masuda [d], Yu Ait Bamai [a,e], Yasuaki Saijo [f], Yoshiya Ito [g], Shoji F Nakayama [h], Michihiro Kamijima [i], Reiko Kishi [a,*], the Japan Environment, Children's Study JECS Group

[a] Center for Environmental and Health Sciences, Hokkaido University, North-12, West-7, Kita-ku, Sapporo 060-0812, Japan
[b] Division of Epidemiological Research for Chemical Disorders, Research Center for Chemical Information and Management, National Institute of Occupational Safety and Health, 6-21-1, Nagao, Tama-ku, Kawasaki 214-8585, Japan
[c] Faculty of Health Sciences, Hokkaido University, North-12, West-5, Kita-ku, Sapporo 060-0812, Japan
[d] Pharmaceutical Sciences, Musashino University, 1-1-20 Shinmachi, Nishitokyo, Tokyo 202-8585, Japan
[e] Department of Pharmaceutical Sciences, University of Antwerp, University Square 1, 2610 Wilrijk, Belgium
[f] Division of Public Health and Epidemiology, Department of Social Medicine, Asahikawa Medical University, 1-1-1 Midorigaoka-higashi-2-jo, Asahikawa 078-8510, Japan
[g] Faculty of Nursing, Japanese Red Cross Hokkaido College of Nursing, 664-1 Akebono-cho, Kitami 090-0011, Japan
[h] Japan Environment and Children's Study Programme Office, National Institute for Environmental Studies, 16-2 Onogawa, Tsukuba 305-8506, Japan
[i] Department of Occupational and Environmental Health, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467-8601, Japan

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ABSTRACT

Kawasaki disease (KD) is common among pediatric patients and is associated with an increased risk of later cardiovascular complications, though the precise pathophysiology of KD remains unknown. Per- and polyfluoroalkyl substances (PFAS) have gathered notoriety as the causal pathogens of numerous diseases as well as for their immunosuppressive effects. The present epidemiological study aims to assess whether PFAS may affect KD risk. We evaluated research participants included in the ongoing prospective nationwide birth cohort of the Japan Environment and Children's Study (JECS). Among the over 100,000 pregnant women enrolled in the JECS study, 28 types of PFAS were measured in pregnancy in a subset of participants (N = 25,040). The JECS followed their children born between 2011 and 2014 (n total infants = 25,256; n Kawasaki disease infants = 271), up to age four. Among the 28 types of PFAS, those which were detected in >60 % of participants at levels above the method reporting limit (MRL) were eligible for analyses. Multivariable logistic regressions were implemented on the seven eligible PFAS, adjusting for multiple comparison effects. Finally, we conducted Weighted Quantile Sum (WQS) and Bayesian kernel machine regression (BKMR) to assess the effects of the PFAS mixture on KD. Therefore, we ran the BKMR model using kernel mechanical regression equations to examine PFAS exposure and the outcomes of KD. Upon analysis, the adjusted multivariable regression results did not reach statistical significance for the seven eligible substances on KD, while odds ratios were all under 1.0. WQS regression was used

Abbreviations: ATSDR, Agency for Toxic Substances and Disease Registry; BKMR, Bayesian kernel machine regression; BMI, Body mass index; CDC, Centers for Disease Control and Prevention; CI, Confidence interval; COVID-19, Coronavirus disease 2019; eGFR, estimated glomerular filtration rate; FDR, False Discovery Rate; IL-6, Interleukin-6; IL-10, Interleukin-10; IFN-γ, Interferon-γ; JECS, Japan Environment and Children's Study; KD, Kawasaki disease; LCMRL, Lowest concentration minimum reporting level; LC-MS/MS, Liquid chromatography tandem mass spectrometry; MRL, Method reporting limit; PFAS, Per- and polyfluoroalkyl substances; PFCAs, Perfluoroalkyl carboxylic acids; PFOA, Perfluorooctanoic acid; PFOS, Perfluorooctanesulfonic acid; PFNA, Perfluorononanoic acid; PFDA, Perfluorodecanoic acid; PFSAs, Perfluoroalkane sulfonic acids; PFUnA, Perfluoroundecanoic acid; PFDoA, Perfluorododecanoic acid; PFTrDA, Perfluorotridecanoic acid; PFHxS, Perfluorohexane sulfonic acid; PPAR, peroxisome proliferator-activated receptors; Q, Quartile; QC, Quality control; TNF-α, Tumor necrosis factor-α; WQS, Weighted Quantile Sum.

* Corresponding author at: Center for Environmental and Health Sciences, Hokkaido University, North-12, West-7, Kita-ku, Sapporo 060-0812, Japan.
E-mail address: rkishi@med.hokudai.ac.jp (R. Kishi).

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to estimate the mixture effect of the seven eligible PFAS, revealing a negative correlation with KD incidence; similarly, BKMR implied an inverse association between the PFAS mixture effect and KD incidence. In conclusion, PFAS exposure was not associated with increased KD incidence.

1. Introduction

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is a serious pediatric disease which is associated with increased risk of later cardiac complications. Much remains unknown about KD, including many questions about its etiology and pathology. KD presents as a systemic vasculitis that predominantly affects children under 5 years old (Wu et al., 2017). KD patients may develop coronary artery aneurysms (Chinawa et al., 2017), which appear in 25 % of untreated KD children (McCrindle et al., 2017). The cardiac complications of KD are associated with reduced myocardial contractility, heart failure, myocardial infarction, arrhythmias, and peripheral arterial occlusion appearing as patients age (An et al., 2021; Sundel et al., 2019). Although treatments for KD such as intravenous immunoglobulin are available, both the exact incidence of KD and methods of prevention are poorly understood.

The prolific research into KD, spanning fields including immunity, pathology, and epidemiology, has shown that there are geographical variations in KD incidence. Since Dr. Tomisaku Kawasaki presented the first case of KD in 1967, KD incidence has appeared to increase (Wu et al., 2017). Clinicians often encounter KD among children in East Asia (Sundel et al., 2017). Incidence rates vary from country to country, with the highest rates reported in Northeast Asia. The annual incidence rate of KD is reported to be approximately 200 cases per 100,000 in Japan, suggesting that circa one out of 100 children will contract KD by age 4–5 (Elakabawi et al., 2020; Nakamura et al., 2012). Because Kawasaki disease primarily develops in young children up to 5 years old, an annual incidence of 200 cases per 100,000 suggests that there are approximately 1,000 total cases per 100,000 during the first 5 years of life among this age group. In contrast, the lowest rates are reported in Sub-Saharan Africa (Elakabawi et al., 2020). The Centers for Disease Control and Prevention (CDC) reports that surveys in the United States show the incidence of KD to be approximately 9–20 per 100,000 children under five years of age ("About Kawasaki disease, (Kawasaki, 2020)"; CDC, 2023). Even in the United States, medical expenses associated with KD are substantial. In 2016, there were approximately 5,440 reported hospitalizations for KD in the United States, leading to an annual national KD admissions cost in the range of $38 million to $110 million (Robinson et al., 2022). Hence, new insights into KD incidence and potential prevention strategies may have wide clinical applications.

Efforts to better understand KD pathology are currently ongoing. Some studies have suggested risk factors for KD including viral pathogens, sex, age, and genetic and environmental predisposition (Fukuda et al., 2021; Noval Rivas and Arditi, 2020; Sundel et al., 2017). Recent studies have also revealed that inflammation and immune responses are involved in KD pathology (Noval Rivas and Arditi, 2020). Multiple studies have reported inflammation of blood vessels, and immunologic abnormalities have been implicated to a greater or lesser extent as part of the mechanism of KD. Necrotizing arteritis is reported to develop within the first two weeks of disease onset, accompanied by neutrophilic infiltration and gradual destruction of the intima, tunica media, and part of the outer membrane of the coronary arteries (Noval Rivas and Arditi, 2020). Recently, genetic and transcriptomic analyses and experiments using mouse models have suggested that IL-1β plays an essential role in KD pathogenesis, especially IL-1β in the bowels (Noval Rivas and Arditi, 2020). In recent years, diseases of the immune system are increasingly thought to be influenced by environmental factors, including per- and polyfluoroalkyl substances (PFAS).

Over the past decade, PFAS have garnered growing attention, both among researchers and the general public, as they are reportedly linked with multiple diseases. While there is geographic variation in PFAS levels, their heavy use in industrial products and processes have made PFAS ubiquitous globally (Valdersnes et al., 2017) (Fenton et al., 2021). Some PFAS affect fetal DNA methylation (Miura et al., 2018) (Kobayashi et al., 2017). PFAS are therefore suspected to be associated with many diseases, including liver failure, thyroid disease, malignant disease, and congenital disabilities (Brennan et al., 2021; Bulka et al., 2021; Guo et al., 2022; Steenland and Winquist, 2021). The earliest PFAS were invented in the 1930s (Head and Jd, 2019). From the 1950s, PFAS found wide use in numerous industrial and commercial applications, including fire extinguishing agents, waxes, paints, cleaning products, and nonstick cookware (Buck et al., 2011; Bulka et al., 2021). Moreover, perfluorooctanesulfonic acid (PFOS), one of the PFAS, has been found to induce tissue inflammation through IL-1β in a mouse model via PPAR pathway (Wang et al., 2021). Given the long history and universal presence of PFAS, potential correlation between PFAS exposure and KD incidence is worth investigating.

Importantly, PFAS have been reported as immunosuppressive substances, suggesting the possibility that PFAS may be inversely correlated with KD incidence. Observational studies in diverse settings have reported findings that support the conclusion that PFAS work as immunosuppressive substances. Perfluorooctanoic acid (PFOA) was reported to have inverse association with IgE levels at birth among girls (Okada et al., 2012). The regional child study in Japan reported that PFOS was inversely related with eczema incidence (Ait Bamai et al., 2020). In Denmark, PFAS exposure was connected with statistically significant decreases in tetanus antibody levels after vaccination among a cohort of five-year-old children (Grandjean et al., 2017). These reports all mention the placental transfer of PFAS from mother to fetus, which suggests the possibility of various health effects occurring in infants as a result of in utero exposure to PFAS. The phenomenon of PFAS suppressing the generation of vaccine antibodies has been reported in other countries – rubella in Norway and mumps and diphtheria in the United States (Grandjean et al., 2012), (Stein et al., 2015). Recently, PFAS exposure was reported to suppress production of Coronavirus disease 2019 (COVID-19) IgG antibodies following COVID-19 vaccination (Kaur et al., 2023). Thus, there is evidence to suggest that PFAS may have immunosuppressive effects on children.

We therefore hypothesize that PFAS may influence KD incidence through their effects on the immune system. This study aims to investigate the association between PFAS and KD incidence using the Japan Environment and Children's Study (JECS), an ongoing and prospective birth cohort study of pregnant Japanese women living in 15 r Regional Centres across Japan. A previous study by Fukuda et al. (2021) using JECS data showed that maternal folic acid deficiency is a risk factor for KD. (Fukuda et al., 2021). Fukuda et al. used data from the same JECS cohort to explore the association between many potential risk factors and KD incidence using logistic regressions.

However, that study did not investigate potential association between maternal PFAS levels and KD incidence. Therefore, assessing the potential correlation between PFAS exposure and KD may have significant public and environmental health ramifications.

2. Material and methods

2.1. Study design and population

We analyzed data from the JECS, an ongoing prospective birth cohort study. The precise methodology of the JECS has been described by Kawamoto et al. (Kawamoto et al., 2014). In summary, pregnant

women were recruited from 15 Regional Centres across Japan over a period of 3 years from 2011 to 2014, producing 103,060 pregnancies (104,062 fetal records) in the JECS (jecs-ta-20190930 and jecs-qa-20210401 datasets). The study flow chart is presented in Fig. 1. Among the whole JECS cohort, inclusion criteria for the present study were measurement of maternal plasma PFAS levels, live birth, and follow-up of at least four years postpartum. Among the over 100,000 research participants, approximately one in four were randomly selected for PFAS measurement. Thus, maternal plasma PFAS levels were measured in 25,040 mothers who gave live birth to 25,256 children, who in turn were followed for KD incidence up to age four.

2.2. Assessment of plasma PFAS levels in pregnant mothers

We used maternal plasma samples to measure maternal PFAS levels. The PFAS level measurements were conducted from 2017 to 2018. Every analytical batch included 24 plasma samples along with 8 calibration solutions, 2 duplicate samples, 2 method blanks, 2 sequence blanks, 2 intermediate calibration point solutions and 3 quality control (QC) samples. The JECS measured the maternal PFAS levels in early pregnancy. Full names of analytes, their abbreviations, and PFAS level distributions are presented in Table 2. The measurement protocol has been previously reported by Nakayama et al. (2020). (Nakayama et al., 2020) Protein precipitation, automatic solid phase extraction pre-treatment, and column-switching liquid chromatography tandem mass spectrometry were employed to detect PFAS levels.

A detailed description of our method validation process is described in Nakayama et al., 2020 (Nakayama et al., 2020). Briefly, for method validation and QC, we used pooled plasma samples prepared from 50 individual samples donated by the Japanese Red Cross. The linear calibration curve was established using seven calibration points ranging from 0.04 to 20 ng/ml. The method detection limit (MDL) and lowest concentration minimum reporting level (LCMRL) were determined by analyzing distilled water fortified with four different concentrations of each PFAS, using 7 replicates for each concentration. Intra-day and inter-day repeatability were evaluated as relative standard deviation with four reference standards (0.4, 4, 8, 12 ng/ml) with 5 replicates and same-day fortified plasma samples, over 5 days respectively. Additionally, the recoveries of target analytes were determined by subtracting the PFAS concentrations in QC plasma that was not fortified from those in fortified QC plasma at concentrations of 0.4, 4, 8, and 12 ng/ml. Linearity, MDL, LCMRL, repeatability, reproducibility, recoveries and ionization interferences were determined using three different liquid chromatography tandem mass spectrometry (LC-MS/MS) systems in a single laboratory. Additionally, we evaluated the accuracy of the analytical method by analyzing a standard reference human serum sample (SRM 1957). To confirm robustness and reliability, the QC sample and SRM 1957 were analyzed across seven different instruments in three separate laboratories. To track potential carry-over contamination and sensitivity drift, we processed two blanks (distilled water) using the same procedure as for the samples, injecting them alongside mid-range calibration solution after every tenth sample. Duplicate analysis was performed at the same interval of every tenth sample. QC was maintained by constructing Shewhart control charts, following ISO 7870 guidelines, and analyzing two pooled plasma samples within each analysis.

2.3. Kawasaki disease incidence follow-up in children

The primary outcome was the incidence of KD from infancy to age four. In brief, presence of KD was evaluated by confirming diagnoses with physicians after mothers reported KD by checking a box on a self-administered questionnaire. The JECS followed all participants up to age four, confirming KD incidence through questionnaires completed by parents a total of 6 times, when the children were 6 months, 1 year, 1.5 years, 2 years, 3 years, and 4 years old. When the JECS received responses from parents indicating KD onset when the children were 2 or 4 years old, the JECS sent a KD-specific questionnaire to the hospital where the child with KD was admitted and requested the hospital physicians to complete the questionnaire providing details on the KD diagnosis.

2.4. Statistical analysis and covariates

We first used descriptive statistics to assess the basic characteristics of mothers and children and evaluated PFAS levels in maternal blood

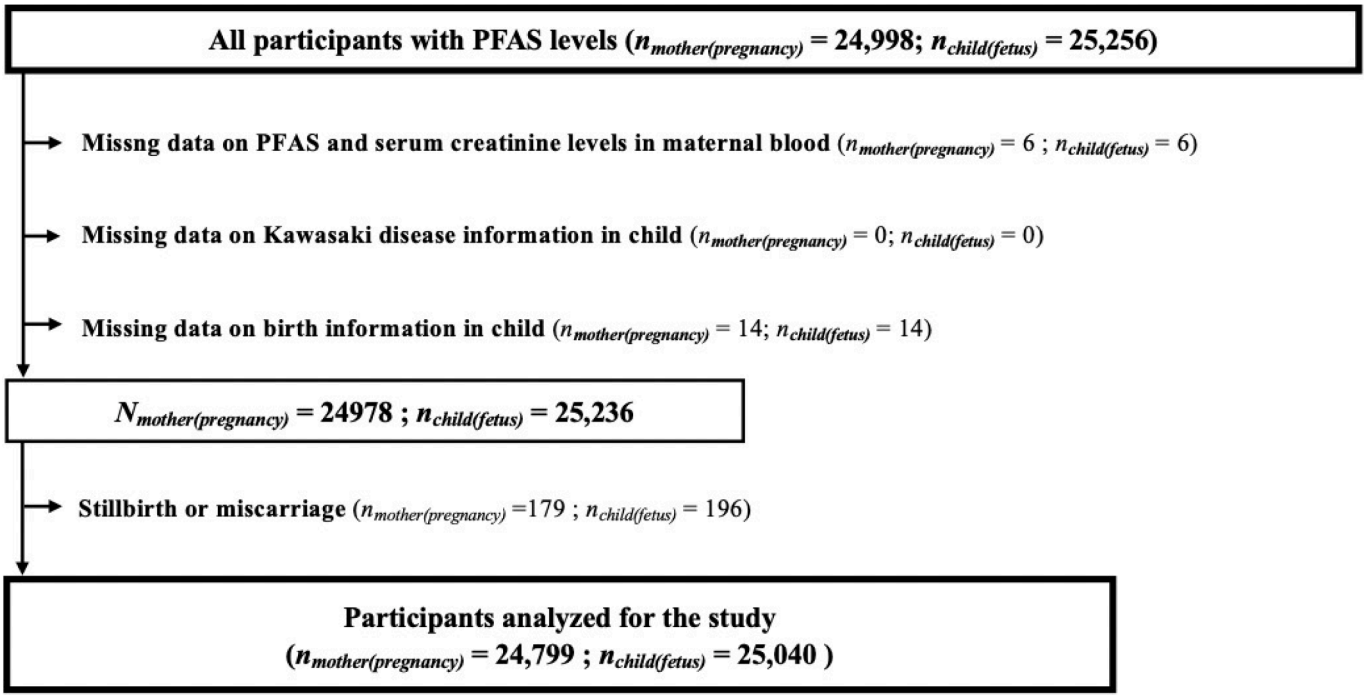

Fig. 1. Study participants flow chart.

and KD information of children at age four. The PFAS whose method reporting limits (MRL) were more than 60 % were eligible for the next statistical analyses. And, the individual PFAS data less than MRL were replaced to half of the individual MRL (Mulhern et al., 2021).

Our statistical analysis employed univariable and multivariable logistic regressions. The individual PFAS levels were $\log_2$ transformed for statistical analyses (Shearer et al., 2021). Each model odds ratio is expressed as a per log unit increase in PFAS substances. The dependent variable was KD incidence, and the independent variables were individual PFAS levels. We collected information about potential covariates considering previous research on KD incidence using data from the JECS (Fukuda et al., 2021) and other studies of KD or PFAS (Huang et al., 2019; Kuo et al., 2022; Sagiv et al., 2018; Verner et al., 2015; Wong et al., 2022) We conducted the multivariable regressions adjusting for maternal age at pregnancy as a continuous variable, maternal folic acid level at second or third trimester as continuous variable, and family income categorized into 7 steps as an ordinal variable. The selection of these three variables was supported by a DAG (Supplement Fig. 1) and evidence of association: maternal age (Huang et al., 2019; McAdam and Bell, 2023), folic acid (Fukuda et al., 2021; Jonker et al., 2020; Zhang et al., 2023), and family income (Azad et al., 2012; Lewin et al., 2017; Zissimopoulou et al., 2020). As a sensitivity analysis, we conducted analysis using a multivariable regression model adjusting for maternal age, maternal BMI, maternal eGFR, maternal smoking history, maternal allergy history, maternal folic acid level, child sex, child body weight less than 2500 g at birth, and family income. We used the following eGFR estimation formula: eGFR (ml/min/1.73 m^2) = 194 × creatinine $(mg/dL)^{-1.094}$ × $age^{-0.287}$ × 0.739 (Okada, 2018).The details of our covariate profiles are shown in Supplement Material 1. Furthermore, the individual univariable regression models were also evaluated by dividing the PFAS substances into quartiles (Q1 – Q4), placing the reference variables in Q1. For multiple comparison, False Discovery Rate (FDR) correction using the Benjamini-Hochberg procedure was used in both the univariable and multivariable regression models. We defined q-values under 0.05 as statistically significant. An additional analysis used Weighted Quantile Sum (WQS) regression and Bayesian kernel machine regression (BKMR) to investigate the overall mixture effect of the eligible PFAS. WQS regression allows assessment of the overall mixture effect of environmental substances while avoiding issues with collinearity among variables. BKMR is a nonparametric approach that enables exploration of the mixture effects of micro-substance exposure on health outcomes (Bobb et al., 2018). Because the present study includes over 20,000 participants, we conducted the BKMR following Takatani et al., who also conducted BKMR with the JECS cohort (Takatani et al., 2022). To adjust for the computational burden caused by the complexity of BKMR, a data subset was established by randomizing 10 % of the original PFAS data. We divided the 7 eligible PFAS substances into 2 groups: perfluorocarboxylic acids (PFCAs) or perfluoroalkane sulfonic acids (PFSAs). Our statistical analyses were performed using R software (Version 4.2.3) and the R packages “gWQS” (Renzetti et al., n.d.) and “bkmr”(Bobb and Bobb, 2017).

2.5. Ethics

The JECS protocol was reviewed and approved by the Japanese Ministry of the Environment’s Institutional Review Board on Epidemiological Studies (No. 100910001) and the Ethics Committees of all participating institutions. JECS was conducted after obtaining written informed consent from all participants. This study was conducted in accordance with the Declaration of Helsinki and its revisions.

3. Results

Participant characteristics are shown in Table 1. Median maternal age was slightly above thirty in both the KD group and the non-KD group. There were no apparent differences in maternal BMI, creatinine, eGFR, folic acid level, or allergy history between groups. The maternal smoking rate was numerically lower in the KD group compared to the non-KD group. A numerically higher number of male children developed KD. Children with congenital abnormalities one month after birth and those with low birth weight were numerically more common in the KD group. The KD group also had numerically more high-income families than the non-KD group. Recurrent KD was found in only three out of 271 children who developed KD.

Among the 28 PFAS measured, seven substances had MRL over 60 % which are summarized in Table 2. Individual levels of all 28 PFAS are included in supplement table1. The seven eligible PFAS in the further analysis: PFOA, Perfluorononanoic acid (PFNA), Perfluorododecanoic acid (PFDA), Perfluoroundecanoic acid (PFUnA), Perfluorotridecanoic acid (PFTrDA), Perfluorohexane sulfonic acid (PFHxS), and PFOS. Median PFOA and PFOS levels were 1.60 and 2.90 ng/ml, respectively. Median levels of PFNA, PFDA, PFHxS, and PFUnA were 1.40, 0.49, 0.33, and 1.10 ng/ml, respectively. These six substances had MRL of over 90 %. In contrast, PFTrDA was detected at levels above MRL in 78.5 % of participants.

We implemented univariable and multivariable regressions on the relationship between KD incidence and exposure to the seven eligible PFAS (Table 3). Univariable regression for PFOS and PFOA found odds ratios of 0.839, 95 % confidence interval (CI) [0.710–0.993] and 0.894; 95 % CI [0.784–1.018], respectively. Odds ratios for the other eligible PFAS were all less than 1.0, with 95 % CI extending above 1.0. Our sensitivity analysis also revealed odds ratios of less than 1.0, though none were statistically significant (Supplement Table 2). The same trend appeared in the multivariable regression results. Although the 95 % CI extended above 1.0 for all PFAS, the odds ratios were under 1.0 ranging from 0.83 to 0.91. The quartile regression model results are summarized in Table 4.

WQS regression results are presented in Table 5 and Fig. 2**.** The univariable negative-effect WQS regression for KD incidence found an odds ratio of 0.860; 95 % CI [0.743–0.994], $p = 0.048$. The weights of PFOA, PFTrDA, PFHxS, and PFOS were all above 0.143 (1.0 divided by 7). The univariable positive-effect WQS regression for KD incidence found an odds ratio of 0.987; 95 % CI [0.877–1.113], $p = 0.841$. Multivariable negative-effect WQS found an odds ratio of 0.862; 95 % CI [0.742–0.999], $p = 0.050$, and multivariable positive-effect WQS found an odds ratio of 0.967; 95 % CI [0.845–1.105], $p = 0.622$**.**

The results of BKMR are shown in Fig. 3, Fig. 4**,** and Supplement Table 3. Fig. 3 implies an inverse association between maternal PFAS levels and KD incidence. Moreover, Fig. 4 suggests that our BKMR results were consistent with the WQS results in that the PFAS mixture has an inverse association with KD incidence.

4. Discussion

The logistic regressions employed in the present study did not reveal statistically significant associations between exposure to individual PFAS and KD incidence, suggesting that individual PFAS did not increase the KD incidence. However, all of the odds ratios found in the logistic regressions were under 1.0. Furthermore, the negative-effect WQS regression has a statistically significant result. Our results suggest that PFAS may have an inverse effect on KD incidence, which may be due to their immunosuppressive effects.

These findings suggest that exposure to certain PFAS may be negatively correlated with KD incidence. However, potential mechanisms for the immunosuppressive effects caused by PFAS are still under investigation. Some PFAS may be agonists of peroxisome proliferator-activated receptors alpha (PPARα) and gamma (PPARγ) (Itoh et al., 2022; Power et al., 2013; Stein et al., 2013). Peroxisome proliferator-activated receptors (PPARs) comprise the nuclear steroid receptor superfamily and include three isoforms: PPAR-α, PPAR-β/δ, and PPAR-γ (Zhang and Young, 2002). They regulate a variety of genes that in turn modulate lipid metabolism fatty acid oxidation, cell metabolism, and immune

Table 1
Participant characteristics of the present study.

	Non-Kawasaki disease group	Kawasaki disease group	The study overall	Full JECS cohort
	(N = 24,769)	(N = 271)	(N = 25,040)	(N = 104,059)
Mother age, years				
Median [Q1, Q3]	31.0 [28.0, 35.0]	32.0 [29.0, 35.0]	31.0 [28.0, 35.0]	31.0 [28.0, 35.0]
Missing	1 (0.0 %)	0 (0 %)	1 (0.0 %)	2,111 (2.0 %)
Maternal pre-pregnancy BMI, kg/m^2				
Median [Q1, Q3]	20.5 [19.1, 22.5]	20.1 [19.0, 22.3]	20.5 [19.1, 22.5]	31.0 [28.0, 35.0]
Missing	22 (0.1 %)	0 (0 %)	22 (0.1 %)	678 (0.7 %)
Maternal creatinine (mg/dl)				
Median [Q1, Q3]	0.440 [0.400, 0.490]	0.440 [0.400, 0.490]	0.440 [0.400, 0.490]	Not available
Maternal eGFR, ml/min/1.73 m^2				
Median [Q1, Q3]	131 [117, 146]	130 [116, 146]	131 [117, 146]	Not available
Missing	1 (0.0 %)	0 (0 %)	1 (0.0 %)	
Maternal folic acid level (mg/dl)				
Median [Q1, Q3]	6.00 [4.20, 10.0]	6.20 [4.20, 10.7]	6.00 [4.20, 10.0]	5.80 [4.00, 9.60]
Missing	339 (1.4 %)	1 (0.4 %)	340 (1.4 %)	6,563 (6.3 %)
Maternal allergy history				
No	14,366 (58.0 %)	152 (56.1 %)	14,518 (58.0 %)	58,236 (56.0 %)
Yes	10,221 (41.3 %)	118 (43.5 %)	10,339 (41.3 %)	42,558 (40.9 %)
Missing	182 (0.7 %)	1 (0.4 %)	183 (0.7 %)	3,265 (3.1 %)
Maternal thyroid disease history				
No	505 (2.0 %)	7 (2.6 %)	512 (2.0 %)	1,978 (1.9 %)
Yes	24,082 (97.2 %)	263 (97.0 %)	24,345 (97.2 %)	98,816 (95.0 %)
Missing	182 (0.7 %)	1 (0.4 %)	183 (0.7 %)	3,265 (3.1 %)
Maternal smoking status				
Smoker	4,312 (17.4 %)	40 (14.8 %)	4,352 (17.4 %)	17,944 (17.2 %)
Non-smoker	19,987 (80.7 %)	230 (84.9 %)	20,217 (80.7 %)	80,224 (77.1 %)
Missing	470 (1.9 %)	1 (0.4 %)	471 (1.9 %)	5,891 (5.7 %)
Child sex				
Male	12,765 (51.5 %)	150 (55.4 %)	12,915 (51.6 %)	51,843 (49.8 %)
Female	12,004 (48.5 %)	121 (44.6 %)	12,125 (48.4 %)	49,140 (47.2 %)
Missing	0 (0 %)	0 (0 %)	0 (0 %)	3,076 (3.0 %)
Child congenital abnormality 1 month after birth				
No	2,252 (9.1 %)	32 (11.8 %)	2,284 (9.1 %)	9,115 (8.8 %)
Yes	21,940 (88.6 %)	233 (86.0 %)	22,173 (88.6 %)	88,296 (84.9 %)
Missing	577 (2.3 %)	6 (2.2 %)	583 (2.3 %)	6,648 (6.4 %)
Child low birth weight below 2500 g at birth				
No	22,429 (90.6 %)	241 (88.9 %)	22,670 (90.5 %)	90,603 (87.1 %)
Yes	2,325 (9.4 %)	29 (10.7 %)	2,354 (9.4 %)	10,189 (9.8 %)
Missing	15 (0.1 %)	1 (0.4 %)	16 (0.1 %)	3,267 (3.1 %)
Family income				
High income (≥4 million Japanese yen)	13,817 (55.8 %)	161 (59.4 %)	13,978 (55.8 %)	54,959 (52.8 %)
Low income (<4 million Japanese yen)	9,053 (36.5 %)	96 (35.4 %)	9,149 (36.5 %)	36,949 (35.5 %)
Missing	1,899 (7.7 %)	14 (5.2 %)	1,913 (7.6 %)	12,151 (11.7 %)
Existence of sibling				
No	9,574 (38.7 %)	123 (45.4 %)	9,697 (38.7 %)	3,8762 (37.3 %)
Yes	4,761 (19.2 %)	45 (16.6 %)	4,806 (19.2 %)	19,556 (18.8 %)
Missing	10,434 (42.1 %)	103 (38.0 %)	1,0537 (42.1 %)	45,741 (44.0 %)
Mother's education level college degree or higher				
No	14,674 (59.2 %)	143 (52.8 %)	14,817 (59.2 %)	59,868 (57.5 %)
Yes	9,678 (39.1 %)	125 (46.1 %)	9,803 (39.1 %)	38,550 (37.0 %)
Missing	417 (1.7 %)	3 (1.1 %)	420 (1.7 %)	5,641 (5.4 %)

eGFR; estimated glomerular filtration rate.

function (Zeng et al., 2022). PPAR-α is a selective intracellular fatty acid sensor and is constitutively expressed in T and B lymphocytes (Zeng et al., 2022). PPARα expression is downregulated in T cells following activation, and may be influenced by microenvironmental factors. Hence, PPARα acts as an endogenous inhibitory factor on T cell activation (Jones et al., 2002), (Zeng et al., 2022). On the contrary, the mechanism of PPAR-γ and its role in the immune system remains under investigation. PPAR-γ is expressed in activated T cells, B cells, and monocytes/macrophages (Zhang and Young, 2002), and a recent study has shown that PPAR-γ agonists enhance regulatory T cell responses (Miao et al., 2022). Moreover, another report implies that some PFAS may influence T-cell-dependent antibody response (TDAR) assay results, which are considered to have broad applicability to evaluate immunotoxic potential (DeWitt et al., 2019), (Woodlief et al., 2021). In addition, T cell regulation abnormalities have been pointed out in KD (Jia et al., 2010).

Our hypothesis that maternal PFAS exposure may influence immune function among children requires discussion of the time lag of circa four years between maternal exposure and assessment of KD incidence among children. Two important characteristics of PFAS may suggest a potential mechanism for such interaction. Firstly, placental transfer of various PFAS has been reported. A *meta*-analysis of PFAS placental transfer found that short-chain $C_{6\text{-}8}$ and long-chain $C_{12\text{-}14}$ perfluorocarboxylic acids (PFCAs) have higher transplacental transfer efficiency than medium-chain $C_{9\text{-}11}$ compounds (Appel et al., 2022). In the present study, four PFAS: PFHxS (carbon chain; C_6), PFOA (C_8), PFOS (C_8), and PFTrDA (C_{13}) had high weights on negative WQS regression. These compounds may have been more efficient at crossing the placental barrier, potentially allowing them to affect the children. This exposure to PFAS during pregnancy may lead to fetal programming. PFOS and PFOA are suspected to influence fetal programming of the metabolism by disrupting the endocrine system (Jensen et al., 2020; Sevelsted et al., 2022; Wolf et al., 2012). Perng et al. reviewed the literature related to PFAS and DNA methylation, collecting 11 articles. They report moderate evidence of the associations between prenatal PFAS exposure and DNA methylation at birth, and also one study suggesting that PFAS-associated effects are sustained into childhood (Perng et al., 2023).

Table 2
Individual PFAS levels in maternal blood, ng/d among the 7 eligible PFAS substances.

Substance name	Abbreviation	MRL* range	DF** n (%)	Mean ± SD†	Minimum	25th	Median	75th	Maximum
Perfluorooctanoic acid	PFOA	0.11—0.28	25,037 (99.9)	2.03 ± 1.58	<MRL	1.10	1.60	2.50	45
Perfluorononanoic acid	PFNA	0.094—0.30	25,037 (99.9)	1.60 ± 1.02	<MRL	0.37	1.40	1.90	36
Perfluorododecanoic acid	PFDA	0.093—0.22	24,875 (99.3)	0.58 ± 0.45	<MRL	0.37	0.49	0.68	15
Perfluoroundecanoic acid	PFUnA	0.098—0.27	25,028 (99.9)	1.24 ± 0.61	<MRL	0.20	1.10	1.50	11
Perfluorotridecanoic acid	PFTrDA	0.10—0.22	19,650 (78.5)	0.29 ± 0.15	<MRL	0.20	0.25	0.35	2.1
Perfluorohexane sulfonic acid	PFHxS	0.10—0.33	22,941 (91.6)	0.40 ± 0.28	<MRL	0.24	0.33	0.47	7.3
Perfluorooctane sulfonic acid	PFOS	0.096—0.32	25,039 (99.9)	3.28 ± 1.90	<MRL	2.10	2.90	4.00	39

*MRL; Method reporting limit.
**DF: Detection frequency. Detection frequency is more than MRL.
†SD Standard deviation.

Table 3
Univariable and multivariable regression results between Kawasaki disease incidence and individual PFAS substances.

Univariable regression Substance	Odds ratio	Standard Error	Lower95%CI	Upper95%CI	P-value	q-value**
Perfluorooctanoic acid (PFOA)*	0.894	0.060	0.784	1.018	0.092	0.238
Perfluorononanoic acid (PFNA)*	0.904	0.080	0.760	1.076	0.256	0.358
Perfluorododecanoic acid (PFDA)*	0.917	0.080	0.773	1.087	0.319	0.372
Perfluoroundecanoic acid (PFUnA)*	0.936	0.087	0.781	1.123	0.478	0.478
Perfluorotridecanoic acid (PFTrDA)*	0.888	0.080	0.745	1.058	0.184	0.322
Perfluorohexane sulfonic acid (PFHxS)*	0.878	0.070	0.752	1.026	0.102	0.238
Perfluorooctanesulfonic acid (PFOS)*	0.839	0.072	0.710	0.993	0.041	0.238
Multivariable regression† Substance	Odds ratio	Standard Error	Lower95%CI	Upper95%CI	P-value	q-value**
Perfluorooctanoic acid (PFOA)*	0.890	0.061	0.778	1.019	0.091	0.266
Perfluorononanoic acid (PFNA)*	0.889	0.082	0.742	1.066	0.205	0.287
Perfluorododecanoic acid (PFDA)*	0.901	0.082	0.753	1.077	0.251	0.292
Perfluoroundecanoic acid (PFUnA)*	0.913	0.089	0.755	1.104	0.345	0.345
Perfluorotridecanoic acid (PFTrDA)*	0.866	0.081	0.722	1.040	0.123	0.266
Perfluorohexane sulfonic acid (PFHxS)*	0.889	0.073	0.758	1.044	0.152	0.266
Perfluorooctanesulfonic acid (PFOS)*	0.835	0.074	0.701	0.994	0.043	0.266

*Substance values were $\log_2$ transformed. Because PFAS were $\log_2$ transformed, regression coefficients represent the expected change in dependent variables as a result of a 2-fold change in PFAS levels.
**The False discovery Rate correction (FDR) was implemented.
†Adjusted for maternal age, folic acid level, and family income.
Each model odds ratio is expressed as a per log unit increase in PFAS substances.

Secondly, we believe that maternal PFAS levels are a representative index of PFAS exposure during early life. In 2023, McAdam and Bell (2023) conducted a systematic review of PFAS concentration determinants. They mention several determinant factors for PFAS concentration including race, country of origin, household income, consumer product use, diet, and water consumption. While half-lives of PFAS have been reported to vary (Li et al., 2018; Xu et al., 2020), it is unlikely that the exposure levels in daily life shift substantially between pregnancy period and after delivery for many participants who did not move long-distance and maintained constant lifestyles. Considering the potential for fetal programming and subsequent PFAS exposure, it is conceivable that they might influence KD incidence among children even at age four.

Our results suggest that PFAS may influence KD incidence via their immunosuppressive effects, which is consonant with recent PFAS studies. PFOA exposure has been reported to correlate negatively with serum IgE levels at birth among girls (Okada et al., 2012). PFOS has an inverse association with eczema incidence, and PFDA and PFUnA have inverse associations with rhino-conjunctivitis (Ait Bamai et al., 2020). Moreover, the Centers for Disease Control and Prevention (CDC) and the Agency for Toxic Substances and Disease Registry (ATSDR) have warned that exposure to high concentrations of PFAS may affect the immune system ((for Toxic Substances and Registry, 2020) (for Toxic Substances, 2020).

Several studies discuss the role of the immunosuppressive effects of PFAS in the development of KD and explain a potential mechanism via TNF-α and helper T cell function. While the pathogenesis of KD has yet to be entirely elucidated, many researchers believe that dysregulation of the immune system and T-cell dysfunction are the main pathophysiological features of patients with KD (Matsubara et al., 2005; Wang et al., 2020). Firstly, cytokines such as interferon-γ (IFN-γ), interleukin-6 (IL-6), interleukin-10 (IL-10) and tumor necrosis factor-α (TNF-α) are involved in KD incidence (Kobayashi et al., 2004; Wang et al., 2020). PFAS may influence immunosuppression via the peroxisome proliferator-activating receptor (PPAR) pathway. PPARs are members of the steroid hormone nuclear receptor superfamily and are involved in the immune system (Tyagi et al., 2011). Wang et al. suggested an association between PFAS and the PPAR pathway in a mouse model (Wang et al., 2014). Among the PPARs (PPAR-α, PPAR-β/δ, and PPAR-γ) PPAR-γ is impacted by PFAS (Almeida et al., 2021; Kirk et al., 2018). PPAR-γ exhibits anti-inflammatory and anti-fibrotic effects, and is involved in TNF-α regulation (Liu et al., 2020; Ye, 2008).

Secondly, exposure to PFOA and PFOS reportedly increases T helper cell type 2 (Th2) cytokine production and suppresses T helper cell type 1 (Th1) cytokine production (Ait Bamai et al., 2020; Dong et al., 2011). Abnormal balance of Th1/Th2 plays an important role in developing KD (Abe et al., 2008; Hirao et al., 1997; Kuo et al., 2007a, 2007b; Kuo et al., 2009, 2008; Matsubara et al., 1999; Woon et al., 2013). There are other PFAS-induced phenomena, such as antioxidant effects, which may affect immunity (Piva et al., 2022). However, the full range of potential mechanisms of PFAS-associated immunosuppression are still incompletely understood. Because PFAS exposure may cause

Table 4
Quartile regression model results.

Univariable	PFAS quartile range	Odds Ratio	Lower CI	Upper CI	P-Value	Q-value*	Multivariable†	Odds Ratio	Lower CI	Upper CI	P Value	Q-value*
PFOA Q1	0.08 - <1.1	Reference	–	–	–	–	PFDA Q1	Reference	–	–	–	–
PFOA Q2	1.1 - <1.6	0.67	0.48	0.95	0.02	0.21	PFDA Q2	0.71	0.5	1.01	0.06	0.45
PFOA Q3	1.6 - <2.5	0.94	0.69	1.27	0.68	0.82	PFDA Q3	0.95	0.69	1.3	0.75	0.92
PFOA Q4	2.5—45	0.66	0.47	0.92	0.02	0.21	PFDAQ4	0.65	0.46	0.92	0.02	0.42
PFNA Q1	0.11 - <0.37	Reference	–	–	–	–	PFDA Q1	Reference	–	–	–	–
PFNA Q2	0.37 - <1.4	0.97	0.71	1.34	0.87	0.91	PFDA Q2	0.96	0.69	1.33	0.81	0.92
PFNA Q3	1.4 - <1.9	1.06	0.76	1.47	0.74	0.82	PFDA Q3	1.05	0.74	1.48	0.79	0.92
PFNA Q4	1.9—36	0.8	0.56	1.14	0.22	0.58	PFDA Q4	0.76	0.53	1.11	0.15	0.45
					0.37	1.4	1.9	36				
PFDA Q1	0.05 - <0.37	Reference	–	–	–	–	PFDA Q1	Reference	–	–	–	–
PFDA Q2	0.37 - <0.49	1.11	0.8	1.56	0.53	0.82	PFDA Q2	1.17	0.83	1.65	0.38	0.82
PFDA Q3	0.49 - < 0.68	1.14	0.82	1.59	0.43	0.82	PFDA Q3	1.09	0.77	1.55	0.61	0.92
PFDA Q4	0.68—15	0.94	0.66	1.34	0.74	0.82	PFDA Q4	0.96	0.67	1.38	0.83	0.92
PFUnA Q1	0.06 - <0.2	Reference	–	–	–	–	PFUnA Q1	Reference	–	–	–	
PFUnA Q2	0.2 - <1.1	1.06	0.76	1.48	0.74	0.82	PFUnA Q2	1.01	0.71	1.43	0.95	0.95
PFUnA Q3	1.1 - <1.5	1.29	0.92	1.79	0.14	0.48	PFUnA Q3	1.28	0.91	1.81	0.15	0.45
PFUnA Q4	1.5—11	0.91	0.63	1.31	0.63	0.82	PFUnA Q4	0.87	0.59	1.27	0.48	0.86
PFTrDA Q1	0.05 - <0.20	Reference	–	–	–	–	PFTrDA Q1	Reference	–	–	–	–
PFTrDA Q2	0.20 - <0.25	1.1	0.8	1.52	0.56	0.82	PFTrDA Q2	1.07	0.77	1.5	0.68	0.92
PFTrDA Q3	0.25 - <0.35	0.78	0.55	1.1	0.16	0.48	PFTrDA Q3	0.77	0.53	1.1	0.15	0.45
PFTrDA Q4	0.35—2.1	0.88	0.63	1.24	0.48	0.82	PFTrDA Q4	0.86	0.6	1.22	0.39	0.82
		0.1				0.24	0.25	0.35	¥			
PFHxS Q1	0.05 - <0.24	Reference	–	–	–	–	PFHxS Q1	Reference	–	–	–	–
PFHxS Q2	0.24 - <0.33	0.73	0.52	1.03	0.07	0.38	PFHxS Q2	0.79	0.56	1.12	0.19	0.5
PFHxS Q3	0.33 - <0.47	0.93	0.68	1.28	0.66	0.82	PFHxS Q3	0.94	0.68	1.31	0.72	0.92
PFHxS Q4	0.47—7.3	0.74	0.53	1.04	0.08	0.38	PFHxS Q4	0.77	0.54	1.1	0.15	0.45
PFOS Q1	0.16 - <2.1	Reference	–	–	–	–	PFOS Q1	Reference	–	–	–	–
PFOS Q2	2.1 - <2.9	0.92	0.67	1.28	0.63	0.82	PFOS Q2	0.89	0.63	1.25	0.49	0.86
PFOS Q3	2.9 - <4	0.98	0.71	1.36	0.91	0.91	PFOS Q3	1.01	0.73	1.41	0.95	0.95
PFOS Q4	4—39	0.74	0.52	1.05	0.09	0.38	PFOS Q4	0.73	0.51	1.04	0.08	0.45

Q1; First quartile, Q2; Second quartile, Q3; Third quartile, Q4; Fourth quartile,
*The False discovery Rate correction (FDR) was implemented.
†Adjusted for maternal age, folic acid level, and family income.

Table 5
Weighted quantile sum regression results.

Model	Odds ratio	Upper 95 %CI	Lower 95 %CI	P-value
Univariable analysis				
Negative β (gWQS*)	0.860	0.743	0.994	0.048
Positive β (gWQS*)	0.987	0.877	1.113	0.841
Multivariable analysis†				
Negative β (gWQS*)	0.862	0.742	0.999	0.050
Positive β (gWQS*)	0.967	0.845	1.105	0.622

*gWQS; proposed method, CI; Confidence interval.
†Adjusted for maternal age, folic acid level, and family income.

immunosuppression even among children, a corresponding decrease in KD incidence may be expected.

The full extent of the immunological effects of various PFAS are not precisely understood. A range of studies have suggested that PFAS are either positively or negatively associated with various target diseases. PFNA exposure negatively affected asthma risk in a Spanish prospective birth cohort study comprising 1,188 children up to 7 years old (Manzano-Salgado et al., 2019). However, studies have reported that PFAS exposure is positively associated with asthma in a Taiwanese cross-sectional child study comprising 300 children aged 10–15 (Qin et al., 2017) (Averina et al., 2019). Furthermore, PFDA was negatively associated with common cold incidence, while PFOA and PFOS were positively associated with lower respiratory tract infections in a Chinese prospective birth cohort study comprising 378 children aged from 10 to 16 years at follow-up (Kvalem et al., 2020). Given this general uncertainty and the lack of statistically significant results in the present study, we believe that further research is warranted to investigate the association between PFAS exposure and KD incidence.

Our results are insufficient to positively assert that individual PFAS can affect KD occurrence, which may suggest gaps in the current understanding of the relationship between IL and 1β and PFAS. Uncertainty remains regarding the mechanisms by which PFAS may interact with IL-1β. Bowel IL-1β is hypothesized to raise intestinal permeability leading to defective intestinal barrier function and systemic immune and autoimmune dysfunction and inflammation in Kawasaki disease (Noval Rivas and Arditi, 2020). Much of the literature on IL-1β and PFOS mentions blood sample concentration, and investigations are ongoing into PFOS concentrations in the bowels. Future studies on the potential relationship between PFAS exposure and KD incidence should investigate the influence of other confounding factors. Of the 28 PFAS included in the JECS data, only seven had MRL over 60 %, suggesting that the remaining 20 substances may require further analysis.

Several factors support the reliability and generalizability of our results. First, the JECS is a nationwide prospective birth cohort study with a large sample size of approximately 100,000 pregnant women, suggesting a relatively small recall bias effect and high generalizability of the study results. Second, JECS participants were randomly selected for PFAS evaluations. Third, KD diagnosis was confirmed directly with local physicians. Fourth, this study took advantage of the precise PFAS

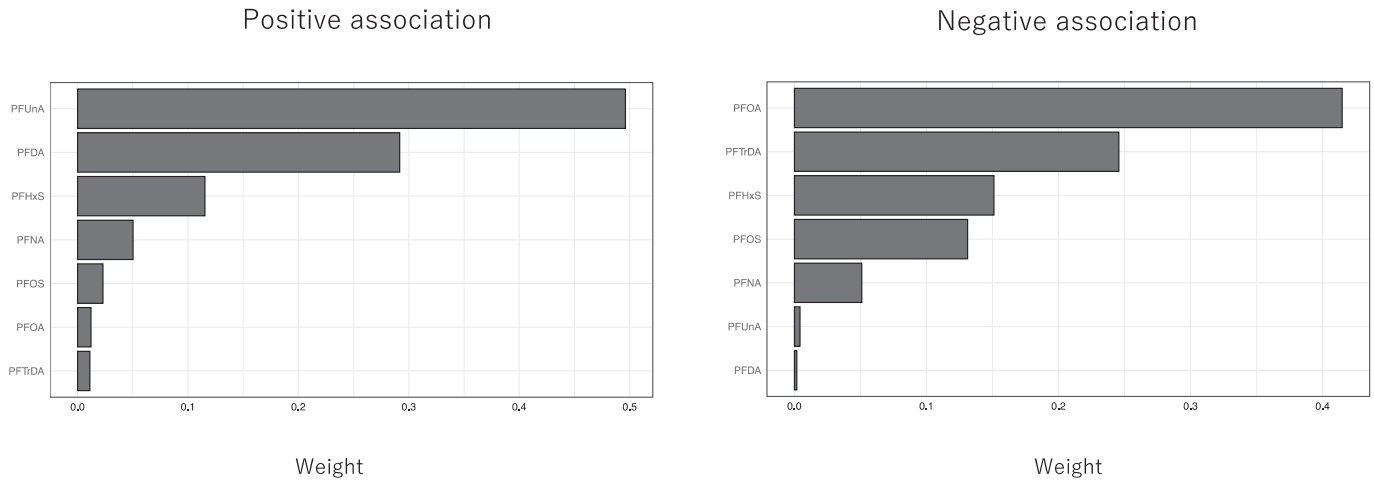

Fig. 2. WQS regression bar plots.

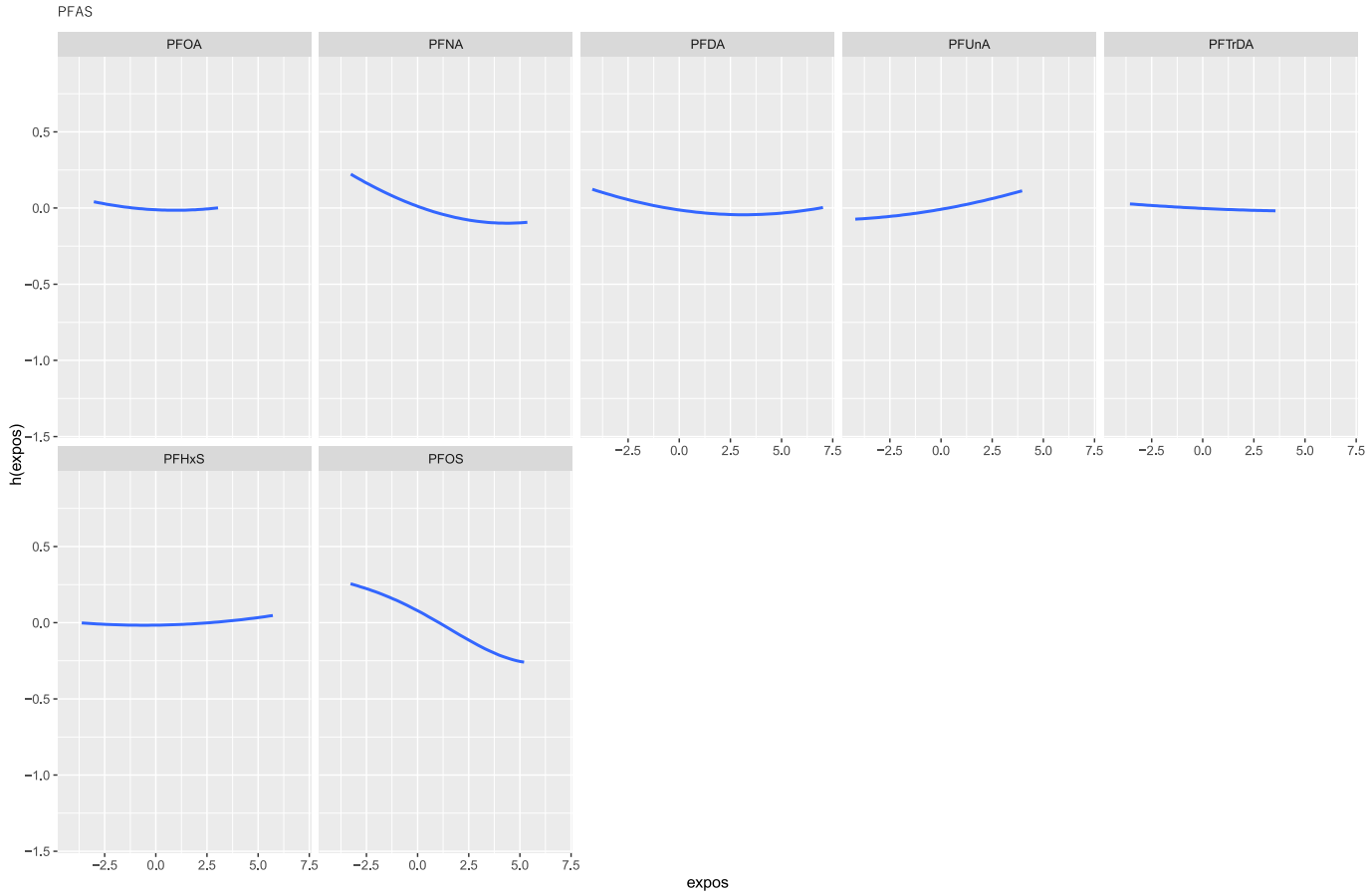

Fig. 3. Bayesian kernel machine regression (BKMR) analysis: multivariable estimation of exposure–response relationships for the associations between PFAS levels and Kawasaki disease incidence. The model was adjusted for maternal age, folic acid level, and family income.

measurement methods developed by Nakayama et al. for the JECS (Nakayama et al., 2020). As a result, our regression analysis results had narrow standard errors. In addition, the mean PFOS level in our study across Japan of 3.28 ng/ml was lower than the general US population in 2017–2018, which is reported to be 4.3 μg/L (ng/ml) (ATSDR, 2020). The tendency toward lower PFOS levels in Japan compared with the US is consistent with the results of PFOS water surveys (Kunacheva et al., 2012).

Despite its strengths, this study also has several important limitations. First, because the etiology of KD remains unknown, potential confounding factors are difficult to determine with certainty. Further, our study examines the association between maternal PFAS exposure levels and KD incidence among their children, but we did not have access to data on PFAS levels among the children at the time of KD onset. Also, while KD diagnoses were performed by local physicians, the accuracy of these diagnoses was not independently confirmed. Furthermore, residual confounding remains a possibility in this observational study, particularly due to the fact that associations with KD risk

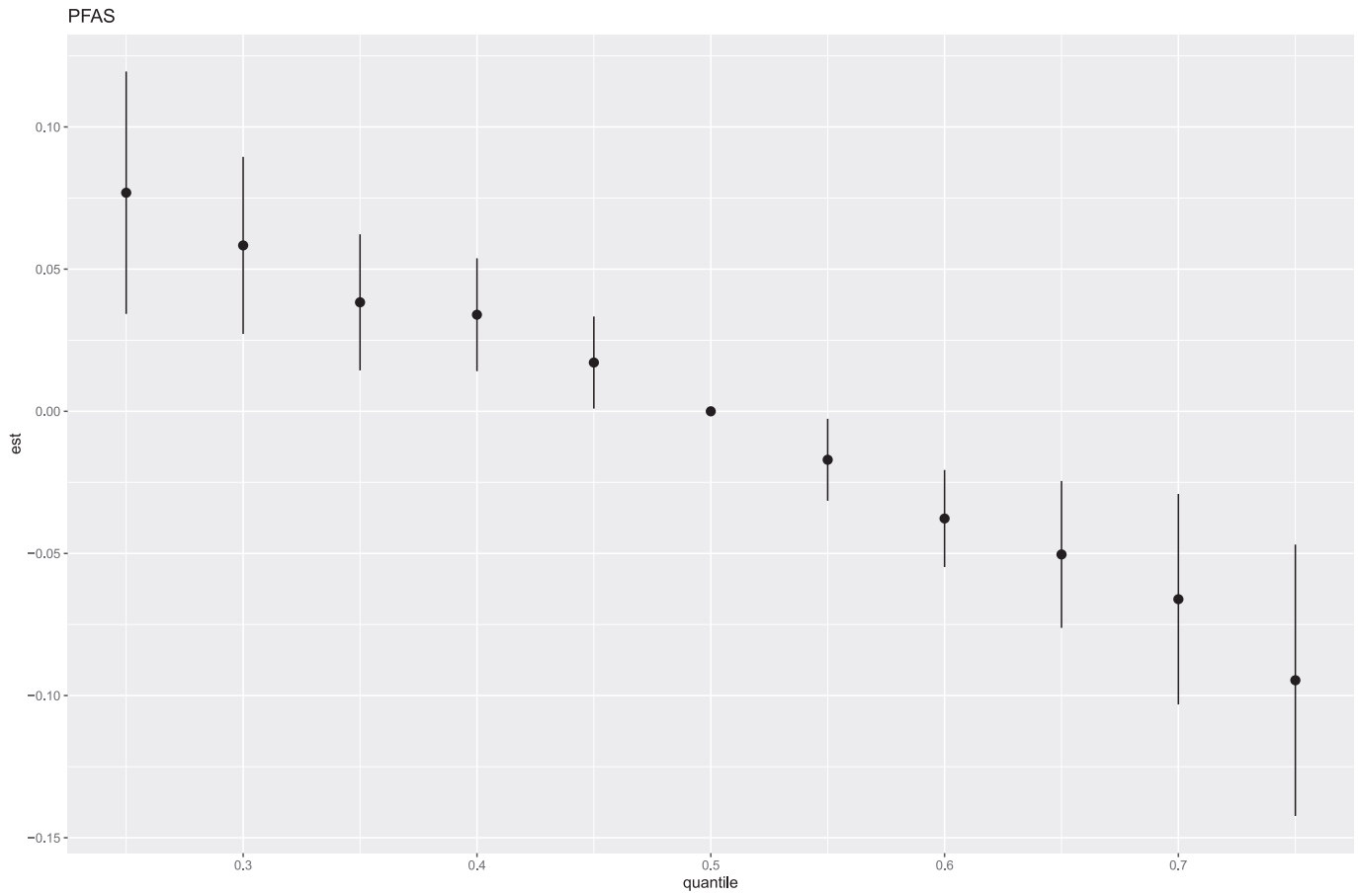

Fig. 4. Overall effect of mixture on Kawasaki disease incidence with all metabolites at their 50th percentile by Bayesian kernel machine regression (BKMR). The model was adjusted for maternal age, folic acid level, and family income.

remain incompletely understood. Lastly, we did not account for developmental changes in the innate immune system, which develops dramatically during the first few years of life (Georgountzou and Papadopoulos, 2017).

5. Conclusion

The present study does not support the conclusion that PFAS exposure increases the incidence of Kawasaki disease.

CRediT authorship contribution statement

Hiroyoshi Iwata: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Sumitaka Kobayashi:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Visualization. **Mariko Itoh:** Investigation, Data curation, Methodology, Formal analysis, Data curation, Writing – review & editing. **Sachiko Itoh:** Investigation, Data curation, Methodology, Formal analysis, Writing – review & editing. **Rahel Mesfin Ketema:** Investigation, Methodology, Formal analysis, Writing – review & editing. **Naomi Tamura:** Investigation, Methodology, Data curation, Formal analysis, Writing – review & editing. **Chihiro Miyashita:** Investigation, Data curation, Formal analysis, Writing – review & editing. **Takeshi Yamaguchi:** Investigation, Methodology, Formal analysis, Writing – review & editing. **Keiko Yamazaki:** Investigation, Methodology, Data curation, Formal analysis, Writing – review & editing. **Hideyuki Masuda:** Conceptualization, Investigation, Writing – review & editing. **Yu Ait Bamai:** Investigation, Writing – review & editing. **Yasuaki Saijo:** Methodology, Investigation, Validation, Resources, Writing – review & editing, Project administration, Funding acquisition. **Yoshiya Ito:** Investigation, Validation, Resources, Writing – review & editing, Project administration, Funding acquisition. **Shoji F Nakayama:** Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Michihiro Kamijima:** Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Reiko Kishi:** Methodology, Investigation, Validation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Declaration of competing financial interests (CFI)

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data statement

Regarding data of the paper publication.
http://www.env.go.jp/chemi/ceh/en/index.html.

Appendix A. . Members of the Japan Environment and Children's study (JECS) group 2023

Members of the JECS Group as of 2023: Michihiro Kamijima (Principal investigator, Nagoya City University, Nagoya, Japan [Aichi Regional Center]), Shin Yamazaki (National Institute for Environmental Studies, Tsukuba, Japan [Programme Office]), Yukihiro Ohya (National Center for Child Health and Development, Tokyo, Japan [Medical Support Center]), Reiko Kishi (Hokkaido University, Sapporo, Japan [Hokkaido Regional Center]), Nobuo Yaegashi (Tohoku University, Sendai, Japan [Miyagi Regional Center]), Koichi Hashimoto (Fukushima Medical University, Fukushima, Japan [Fukushima Regional Center]), Chisato Mori (Chiba University, Chiba, Japan [Chiba Regional Center]), Shuichi Ito (Yokohama City University, Yokohama, Japan [Kanagawa Regional Center]), Zentaro Yamagata (University of Yamanashi, Chuo, Japan [Koshin Regional Center]), Hidekuni Inadera (University of Toyama, Toyama, Japan [Toyama Regional Center]), Takeo Nakayama (Kyoto University, Kyoto, Japan [Kyoto Regional Center]), Tomotaka Sobue (Osaka University, Suita, Japan [Osaka Regional Center]), Masayuki Shima (Hyogo Medical University, Nishinomiya, Japan [Hyogo Regional Center]), Seiji Kageyama(Tottori University, Yonago, Japan [Tottori Regional Center]), Narufumi Suganuma (Kochi University, Nankoku, Japan [Kochi Regional Center]), Shoichi Ohga (Kyushu University, Fukuoka, Japan [Fukuoka Regional Center]), and Takahiko Katoh (Kumamoto University, Kumamoto, Japan [Minami-Kyushu and Okinawa Regional Center]).

Appendix B. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108321.

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