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Prenatal exposure to selenium, mercury, and manganese during pregnancy and allergic diseases in early childhood: The Japan Environment and Children's study

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ABSTRACT

Background: Prenatal exposure to metallic elements may adversely affect early childhood health. However, more evidence is needed as population-based cohort studies are currently limited.
Objectives: We aimed to examine the associations between prenatal metallic (mercury, selenium, and manganese) exposure and the risk of allergic diseases in early childhood until three years of age.
Methods: The data from 94,794 mother-infant pairs, who participated in the Japan Environment and Children's study, were used in this study. Prenatal metallic element exposure was measured in maternal blood collected during mid-pregnancy. The incidence of atopic dermatitis, food allergies, asthma, and allergic rhinitis during the first three years of life was prospectively investigated using self-reports of physician-diagnosed allergies. A multivariable modified Poisson regression model was used to estimate the cumulative incidence ratio and their 95% confidence intervals of allergic diseases associated with prenatal exposure to mercury, selenium, and manganese. We further evaluated the interaction between mercury and selenium exposures in this association.
Results: We confirmed 26,238 cases of childhood allergic diseases: atopic dermatitis, food allergies, asthma, and allergic rhinitis in 9,715 (10.3%), 10,897 (11.5%), and 9,857 (10.4%), 4,630 (4.9%), respectively. No association was found between prenatal mercury or manganese exposure and the risk of allergic diseases. Prenatal selenium exposure was inversely associated with atopic dermatitis, food allergies, allergic rhinitis, and any allergic diseases, but not with asthma. These inverse associations were more pronounced for lower mercury exposures than for higher exposures.

Abbreviations: BMI, body mass index; CIRs, cumulative incidence ratios; Cis, confidence intervals; FFQs, food frequency questionnaires; IQR, interquartile range; JECS, the Japan Environment and Children's Study.

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Conclusions: Our findings suggest that prenatal exposure to selenium may be beneficial for reducing the risk of atopic dermatitis, food allergies, allergic rhinitis, and any allergic diseases in early childhood, especially with lower prenatal mercury exposure.

1. Introduction

Allergic diseases arise from inappropriate immune responses caused by both a genetic predisposition and various environmental factors and can lead to diseases such as atopic dermatitis (also called atopic eczema), food allergies, asthma, allergic rhinitis (Reynolds and Finlay, 2017; Stone, 2003). The Global Burden of Disease Study reported a 15 to 20% prevalence of atopic dermatitis among children (Laughter et al., 2021). Another study conducted in 60 countries showed that the prevalence of atopic dermatitis in children aged six to seven years was 0.9% to 22.5%, showing higher values in Asia and Latin America (Odhiambo et al., 2009). Our Japanese cohort study reported that 7.3% of children are diagnosed with atopic dermatitis within the first three years of life (Yamamoto-Hanada et al., 2020).

Heavy metals are toxic environmental pollutants ubiquitously distributed in food, soil, water, and air pollution (Kathuria and Silverberg, 2016; Sall et al., 2020; Tchounwou et al., 2012). Metallic elements, such as mercury, lead, arsenic, and cadmium, are major environmental pollutants. These metallic elements can have adverse effects on human health, particularly exposure to pregnant women, and their effects on the fetus are a public health concern (Amaya et al., 2013). However, essential trace elements, such as selenium, manganese, zinc, and copper, maintain normal physiological processes and modulate immune system functions (Vas and Monestier, 2008). Mercury, selenium, and manganese readily pass through the placental barrier, which may affect fetal development (Bocca et al., 2019; Iyengar and Rapp, 2001; Li et al., 2019; Rudge et al., 2009). Therefore, prenatal exposure to metallic elements may cause allergic diseases during childhood. Mercury exposure suggests it affects the immune system, and depending on the species of mercury, either an immunosuppressive (due to organic mercury) or an immunostimulatory (due to inorganic mercury) may occur (Havarinasab and Hultman, 2005; Vas and Monestier, 2008). A previous mother–child cohort study conducted in Korea on 690 pregnant women showed that high mercury concentration in maternal cord blood was associated with atopic dermatitis risk in children at 12–24 months of age but not at 24–36 months or 48–60 months (Shin et al., 2019). The association between prenatal selenium exposure and the development of allergies in children remains controversial. A Japanese mother–child cohort study conducted on 834 pregnant women reported that low maternal or infant selenium levels, measured in the hair of the exposed individuals, were associated with an increased risk of atopic dermatitis at ten months of age (Yamada et al., 2013). However, the EDEN prospective cohort study of 861 French pregnant women showed an association between maternal plasma selenium concentrations and the reduced risk of wheezing in children up to three years of age, but not with the risk of asthma, allergic rhinitis, or atopic dermatitis (Baïz et al., 2017). Manganese is an essential trace element with antioxidant properties; however, maternal blood manganese concentrations are associated with a higher risk of developing childhood eczema (Pesce et al., 2021).

Knowledge of the association between prenatal metallic element exposure and the development of allergic diseases in children remains limited. In particular, mercury and selenium have antagonistic interactions (Falnoga and Tusek-Znidaric, 2007; Raymond and Ralston, 2004), and their association with the risk of allergic diseases is uncertain. Therefore, it is necessary to comprehensively examine the impact of prenatal exposure to these metallic elements on children's health. Using large birth cohort data, this study examined whether prenatal exposure to metallic elements, such as mercury, selenium, and manganese, was associated with the development of allergic diseases, such as atopic dermatitis, food allergies, and asthma, among children during the first three years of life.

2. Materials and Methods

2.1. Study design

This study used data from 103,060 pregnancies in an ongoing nationwide prospective study, the Japan Environment and Children's Study (JECS). The JECS protocol has been previously described (Kawamoto et al., 2014; Michikawa et al., 2018). In brief, the JECS recruited women during early pregnancy between January 2011 and March 2014. Setting up 15 Regional Centres, the JECS covers northern and southern parts of Japan. The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (No. 100910001) and the Ethics Committees of all the participating institutions. The JECS was conducted in accordance with the Declaration of Helsinki and all other national regulations after obtaining written informed consent from all participants.

2.2. Data collection and study population

The number of pregnancies recorded in the JECS between 2011 and 2014 was 103,060. Of these, 7,245 participants were excluded because of missing data on metallic elements. Subsequently, the following number of participants were excluded: 869 due to multiple gestations, 151 due to stillbirths and miscarriages, and one subject with missing all variables. After applying the inclusion criteria, 94,794 participants were eligible for the present study (Fig. 1). This study used the jecs-ta-20190930 datasets, released in October 2019.

2.3. Measurement of maternal whole blood metallic elements

The whole blood concentrations of metallic elements, including mercury, selenium, and manganese, were measured using inductively coupled plasma mass spectrometry (ICP-MS), as described previously (Nakayama et al., 2019). Most blood samples (33 mL) were collected from the peripheral vein during the second/third trimesters. Metallic element concentrations in the blood samples were quantified using an Agilent 7,700 inductively coupled plasma mass spectrometer (ICP-MS) with an autosampler (Agilent Technologies, Tokyo, Japan). To measure large samples, the modified alkali dilution method provided by the US Centers for Disease Control and Prevention (CDC, 2008, 2014) was applied instead of the traditional method involving microwave decomposition. All whole blood metallic element levels measured in this study were greater than the detection limit of 0.049, 0.522, and 0.837 ng/g for mercury, selenium, and manganese, respectively (Nakayama et al., 2019). In this study, units of ng/g were used for metallic elements. The mixture density of human blood samples using the modified alkali dilution method was 0.999 g/mL; therefore, "ng/g" units are approximately equal to "μg/L" units.

2.4. Measurement of covariates

Data on birth outcomes and covariates were acquired as previously (Michikawa et al., 2015). We obtained information on maternal age through blood sampling, marital status, annual household income, educational level, employment status, smoking habits, alcohol intake, and history of maternal allergic diseases from the questionnaires; height and weight before pregnancy, and parity from the questionnaires and

medical records transcripts; and delivery outcomes such as gestational duration, and infant sex from medical records transcripts. Body mass index (BMI) was calculated by dividing the body weight in kilograms by the square of the height in meters. Fish intake during pregnancy was determined using food frequency questionnaires (FFQs) completed during the second/third trimesters. FFQs have been validated as self-administered diet questionnaires in previous Japanese epidemiological studies (Yokoyama et al., 2016).

2.5. Definition of an incident on allergic diseases

Outcomes on allergic diseases were collected using self-administered questionnaires among children aged one year, one year and six months, two years, and three years for atopic dermatitis, food allergies, and asthma, and two and three years for allergic rhinitis. For the section "Immune system disorder diagnosed," caregivers responded to the following question of each child's age "Since the last survey, has your child ever been diagnosed with allergic diseases by a physician?" We defined participants as having "any allergic disease " if they were diagnosed with any of the three allergic diseases previously listed.

2.6. Statistical analyses

Modified Poisson regression models with a robust error variance using sandwich estimation (Zou, 2004) were used to assess the association of prenatal metallic element exposure with the cumulative incidence of allergic diseases during the three years since the birth of the child. We estimated cumulative incidence ratios (CIRs) and 95% confidence intervals (CIs) using multivariable modified Poisson regression models. Maternal blood mercury, selenium, and manganese concentrations were treated continuously (log2-transformed) and categorically (using quintiles: lowest = Q1 and highest = Q5). We performed multivariable modified Poisson regression to estimate the CIRs and 95% CIs for each metallic element-outcome association of interest with Q1 as a reference to confirm concentration associations. Test for linear trends used a median value across the quintile of maternal exposure to metallic elements on risks of allergic diseases. Model 1 was adjusted for maternal age and area of residence; model 2 was adjusted further for maternal exposure to metallic elements (mercury, selenium, or manganese) and a gestational week at blood sampling; model 3 was adjusted further for fish intake during pregnancy, pre-pregnancy BMI, lifestyle, socioeconomic factors, previous delivery, gestational duration, maternal history of allergic diseases, and infant sex.

Additionally, a cross-product term for the median of the tertiles of selenium and mercury concentrations was included in the model to assess the interaction between selenium and mercury exposure. We examined the risk of allergic diseases according to tertiles of blood selenium concentration, stratified by tertiles of blood mercury concentration.

The sub-group analysis examined the associations between metallic elements and risks of allergic diseases using modified Poisson regression analysis, stratified by infant sex, maternal age (<30, 30–39, or ≥ 40 years), and maternal history of allergic diseases (none, or any one of the following: atopic dermatitis, food allergies, asthma, or allergic rhinitis, and two or more of their conditions). The effect modification was tested with these covariates by using cross-product terms.

All models were adjusted for the following covariates: maternal age at blood sampling (<20, 20 to < 30, 30 to < 40, and ≥ 40 years), gestational week at blood sampling (16 to < 28 and ≥ 28 weeks), quartile of fish intake (g), pre-pregnancy BMI (<18.5, 18.5 to < 25.0, 25.0 to < 30.0, 30.0 to < 35.0, and ≥ 35.0 kg/m^2), smoking habits during pregnancy (never, previously did, but quit before recognizing

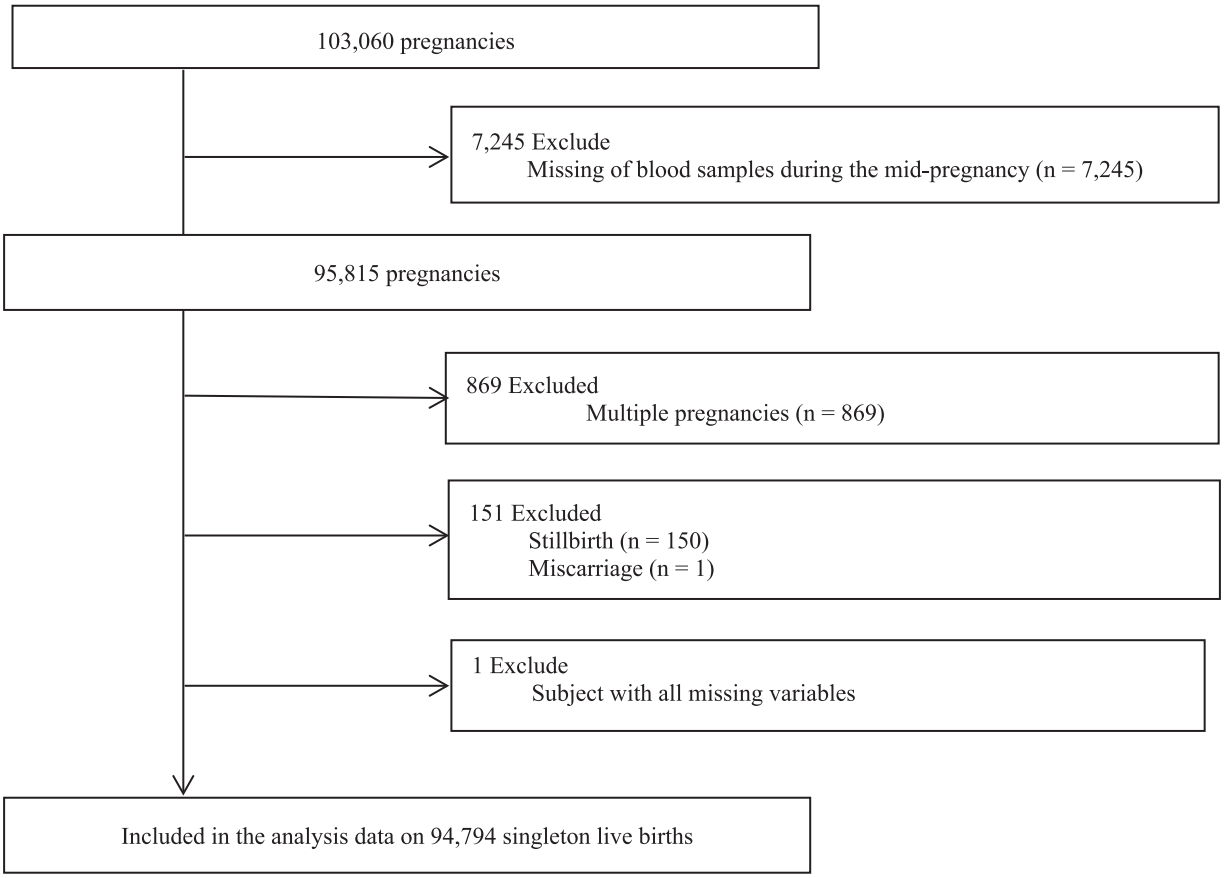

Fig. 1. Flow chart for the study population.

current pregnancy, previously did, but quit after finding out current pregnancy, and currently smoking), alcohol intake during pregnancy (never, ex-drinkers, and currently drinking; ethanol < 150 mL/week, currently drinking; ethanol ≥ 150 mL/week), maternal education levels (<10, 10 to < 13, 13 to < 16, 16, and ≥ 17 years of education), annual household income (<4, 4 to < 6, 6 to < 8, 8 to < 10 and ≥ 10 million Japanese yen [JPY]), marital status (married, never-married, and divorced or widowed), employment status (unemployment and homemaker, part-time worker, self-employed, employment, and ohers), and maternal history of allergies (atopic dermatitis, food allergies, asthma, and allergic rhinitis), parity (0, 1 to 4, and ≥ 5), gestational duration (<37, 37 to < 42, and ≥ 42 week), infant sex. Gestational week at blood sampling was included as a covariate because a previous study using JECS data found an association with metallic element concentrations (particularly manganese concentrations) (Nakayama et al., 2019). The proportions of missing for these covariates were 8.2% in annual household income and 0.02% to 2.7% in other variables. Multivariable modified Poisson regression analysis was performed using multiple imputations with chained equations for missing data for the covariates to avoid selection bias. Fifty imputation datasets were created, and modified Poisson regression analyses were performed on each, with pooled estimates described. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses.

3. Results

The selected baseline characteristics of 94,794 mother–child pairs are shown in Table 1, according to the quintiles of maternal blood mercury, selenium, and manganese concentrations during pregnancy. Higher maternal blood mercury concentrations were positively correlated with maternal age, fish intake, and maternal history of allergic rhinitis. Higher maternal blood selenium concentrations were positively correlated with maternal age, fish intake, pre-pregnancy BMI, and male of infant sex. Higher maternal blood manganese concentrations were positively correlated with pre-pregnancy BMI and male of infant sex and inversely correlated with maternal age. The other baseline characteristics are listed in Table S1.

The distributions of blood metallic elements are shown in Table 2. Median (interquartile range) maternal blood mercury, selenium, and manganese concentrations (ng/g) during pregnancy for participants were 3.6 (2.7), 168.0 (26.0), and 15.4 (6.0), respectively.

We confirmed 26,238 cases of any allergic diseases (atopic dermatitis, food allergies, asthma, or allergic rhinitis) with a three-year cumulative incidence of 28.5%. Atopic dermatitis cases were 9,715, food allergies cases were 10,897, asthma cases were 9,857, and allergic rhinitis cases were 4,630, with a three-year cumulative incidence of 10.3%, 11.5%, 10.4%, and 4.9%, respectively.

Table 3 CIRs and 95% CIs of atopic dermatitis, food allergies, asthma, allergic rhinitis, and any allergic diseases according to log2-transformed maternal blood concentrations of mercury, selenium, and manganese. Modified Poisson regression analysis showed that a twofold increase in maternal blood mercury concentration was associated with a 1 to 4% increase in atopic dermatitis, food allergies, asthma, and all allergic diseases in model 2, but the association disappeared after multivariable adjustment in model 3. A twofold increase in maternal blood selenium concentration was inversely associated with risks of atopic dermatitis, food allergies, allergic rhinitis, and any allergic diseases, but not with asthma in all models. For manganese, no association was found in all models.

The CIRs, and 95% CIs of atopic dermatitis, food allergies, asthma, allergic rhinitis, and any allergic diseases according to quintiles of maternal blood concentrations of mercury, selenium, and manganese are shown in Table 4. Mercury exposure was not associated with the risks of any allergic disease. Selenium exposure was inversely associated with risks of atopic dermatitis, food allergies, allergic rhinitis, and any allergic diseases, but not risks of asthma. No association was observed

Table 1
The selected characteristics of 94,794 mothers-child pairs according to maternal blood mercury, selenium, and manganese during pregnancy.

	Maternal blood mercury concentrations during pregnancy, ng/g, Median (IQR)				
	Q1: 1.8 (0.6)	Q2: 2.8 (0.4)	Q3: 3.6 (0.5)	Q4: 4.8 (0.7)	Q5: 7.2 (2.5)
No. at risk	19,028	18,792	19,140	18,904	18,930
Maternal characteristics					
Age (years), mean (SD)	30.4 (5.3)	30.8 (5.0)	31.0 (5.0)	31.2 (4.9)	31.3 (5.0)
Fish intake during pregnancy (g/day), mean (SD)	24.9 (28.4)	30.4 (30.0)	33.8 (34.6)	37.3 (51.3)	43.1 (50.9)
Pre-pregnancy BMI ≥ 25 kg/m^2, n (%)	1908 (10.0)	1807 (9.6)	1909 (10.0)	2039 (10.8)	2544 (13.4)
History of dermatitis, n (%)	2894 (15.2)	2945 (15.7)	2992 (15.6)	2931 (15.5)	2955 (15.6)
History of food allergies, n (%)	967 (5.1)	923 (4.9)	914 (4.8)	874 (4.6)	837 (4.4)
History of asthma, n (%)	2074 (10.9)	2049 (10.9)	2092 (10.9)	1989 (10.5)	2029 (10.7)
History of allergic rhinitis, n (%)	6483 (34.1)	6546 (34.8)	6812 (35.6)	6826 (36.1)	7080 (37.4)
Birth characteristics of children					
Gestational duration < 37 week, n (%)	816 (4.3)	778 (4.2)	824 (4.3)	846 (4.5)	884 (4.7)
Infant sex, male, n (%)	9723 (51.1)	9557 (50.9)	9690 (50.6)	9631 (50.9)	9797 (51.8)
	Maternal blood selenium concentrations during pregnancy, ng/g, Median (IQR)				
	Q1: 147.0 (9.0)	Q2: 159.0 (5.0)	Q3: 168.0 (5.0)	Q4: 179.0 (6.0)	Q5: 196.0 (15.0)
No. at risk	18,631	18,854	20,002	18,479	18,828
Maternal characteristics					
Age (years), mean (SD)	30.8 (5.2)	30.8 (5.1)	30.9 (5.0)	31.0 (5.0)	31.3 (5.0)
Fish intake during pregnancy (g/day), mean (SD)	30.6 (33.8)	32.9 (52.0)	33.7 (33.1)	35.1 (37.7)	37.3 (44.2)
Pre-pregnancy BMI ≥ 25 kg/m^2, n (%)	1463 (7.9)	1843 (9.8)	2149 (10.7)	2153 (11.7)	2599 (13.8)
History of dermatitis, n (%)	2993 (16.1)	3017 (16.0)	3068 (15.3)	2855 (15.4)	2784 (14.8)
History of food allergies, n (%)	952 (5.1)	981 (5.2)	906 (4.5)	850 (4.6)	826 (4.4)
History of asthma, n (%)	2067 (11.1)	2126 (11.3)	2066 (10.3)	1971 (10.7)	2003 (10.6)
History of allergic rhinitis, n (%)	6602 (35.4)	6724 (35.7)	7083 (35.4)	6657 (36.0)	6681 (35.5)
Birth characteristics of children					
Gestational duration < 37 week, n (%)	810 (4.4)	744 (4.0)	832 (4.2)	846 (4.6)	916 (4.9)
Infant sex, male, n (%)	9462 (50.8)	9605 (50.9)	10,122 (50.6)	9419 (51.0)	9790 (52.0)
	Maternal blood manganese concentrations during pregnancy, ng/g, Median (IQR)				
	Q1: 10.6 (1.9)	Q2: 13.2 (1.1)	Q3: 15.4 (1.1)	Q4: 17.9 (1.5)	Q5: 22.1 (3.7)
No. at risk	19,297	18,521	19,212	18,770	18,994
Maternal characteristics					
Age (years), mean (SD)	31.2 (5.0)	31.1 (5.0)	30.9 (5.0)	30.8 (5.1)	30.7 (5.2)
Fish intake during pregnancy (g/day), mean (SD)	34.0 (34.8)	34.4 (33.4)	34.0 (46.3)	33.4 (31.9)	33.8 (53.0)
Pre-pregnancy BMI ≥ 25 kg/m^2, n (%)	1600 (8.3)	1836 (9.9)	2032 (10.6)	2253 (12.0)	2486 (13.1)
History of dermatitis, n (%)	3101 (16.1)	2890 (15.6)	3017 (15.7)	2858 (15.2)	2851 (15.0)

(continued on next page)

Table 1 (*continued*)

	Maternal blood mercury concentrations during pregnancy, ng/g, Median (IQR)				
	Q1: 1.8 (0.6)	Q2: 2.8 (0.4)	Q3: 3.6 (0.5)	Q4: 4.8 (0.7)	Q5: 7.2 (2.5)
History of food allergies, n (%)	958 (5.0)	916 (4.9)	912 (4.7)	860 (4.6)	869 (4.6)
History of asthma, n (%)	2042 (10.6)	2000 (10.8)	2093 (10.9)	1958 (10.4)	2140 (11.3)
History of allergic rhinitis, n (%)	6905 (35.8)	6493 (35.1)	6968 (36.3)	6702 (35.7)	6679 (35.2)
Birth characteristics of children					
Gestational duration < 37 week, n (%)	848 (4.4)	781 (4.2)	808 (4.2)	804 (4.3)	907 (4.8)
Infant sex, male, n (%)	9503 (49.2)	9351 (50.5)	9770 (50.9)	9789 (52.2)	9985 (52.6)

IQR: interquartile range.
SD: Standard deviation.

between manganese exposure and risks of allergic diseases.

Table 5 shows the associations between prenatal selenium exposure and risks of allergic diseases, stratified by tertiles of mercury exposure. Inverse associations between selenium exposure and the risk of allergic diseases were evident for atopic dermatitis in the lowest and middle tertiles of mercury exposure and for food allergies and any allergic diseases in the lowest tertiles of mercury exposure; *P* for interaction was 0.216, 0.246, and 0.015, respectively. The significant interaction by mercury exposure in the association between selenium exposure and risks of allergic diseases was observed for atopic dermatitis, food allergies, and any allergic diseases, in which the inverse association was evident in the lowest or second tertiles of mercury exposure. An interaction was observed in asthma, but no association with selenium was stratified by mercury concentration.

The results of sub-group analyses stratified by infant sex, maternal age, and maternal history of allergy, and the results are shown in Table S2. The inverse associations between selenium exposure and risks of atopic dermatitis, food allergies, and any allergic diseases were consistently observed in most of the stratified variables. The inverse association between selenium exposure and the risk of allergic rhinitis tended to be more evident for males and 30–39 years of age. The risk of mercury exposure was associated with risk of asthma when there was a history of two or more maternal allergic diseases, but otherwise, no associations were found. For all the stratified variables, no association was observed between manganese exposure and the risk of allergic diseases. Furthermore, no significant interactions between the three metallic elements and risk of allergic diseases were observed for all of the stratified variables.

4. Discussion

To the best of our knowledge, this is the largest prospective birth cohort study to examine the impact of prenatal exposure to metallic elements on the risk of allergic diseases in early childhood. We found inverse associations between prenatal selenium exposure and risks of any allergic diseases, especially atopic dermatitis, food allergies, and allergic rhinitis, but not asthma during the initial three years of life. Such

Table 2
Distributions of maternal blood concentrations of metallic element.

Metallic elements	Mean	SD	Minimum	25th percentile	Median	75th percentile	Maximum
Mercury (ng/g)	4.21	2.49	0.18	2.54	3.64	5.20	58.80
Selenium (ng/g)	170.16	20.34	82.80	156.00	168.00	182.00	976.00
Manganese (ng/g)	15.95	4.66	2.84	12.60	15.40	18.60	60.80

SD: Standard deviation.

Table 3
Cumulative incidence ratios (CIRs) and 95% confidence intervals (CIs) of atopic dermatitis, food allergies, asthma, allergic rhinitis, and any allergic diseases according to log2-transformed maternal blood concentrations of mercury, selenium, and manganese.

		Mercury		Selenium		Manganese	
	n = 94,794	CIR (95%CI)	*P*	CIR (95%CI)	*P*	CIR (95%CI)	*P*
Atopic dermatitis							
No. of cases = 9715	Model1	1.02 (0.99, 1.05)	0.127	0.76 (0.68, 0.85)	<0.001	1.01 (0.97, 1.06)	0.577
	Model2	1.04 (1.01, 1.06)	0.009	0.72 (0.64, 0.82)	<0.001	1.02 (0.98, 1.07)	0.294
	Model3	1.01 (0.99, 1.04)	0.308	0.73 (0.65, 0.83)	<0.001	1.02 (0.97, 1.07)	0.437
Food allergies							
No. of cases = 10,897	Model1	1.01 (0.98, 1.03)	0.513	0.73 (0.65, 0.81)	<0.001	0.98 (0.94, 1.03)	0.446
	Model2	1.03 (1.00, 1.05)	0.034	0.71 (0.63, 0.79)	<0.001	0.99 (0.95, 1.03)	0.659
	Model3	1.00 (0.98, 1.03)	0.938	0.81 (0.72, 0.90)	<0.001	1.00 (0.96, 1.04)	0.902
Asthma							
No. of cases = 9857	Model1	1.03 (1.00, 1.05)	0.031	1.06 (0.95, 1.19)	0.284	1.03 (0.99, 1.08)	0.170
	Model2	1.03 (1.00, 1.05)	0.046	1.02 (0.91, 1.15)	0.709	1.03 (0.99, 1.08)	0.172
	Model3	1.02 (0.99, 1.04)	0.259	0.93 (0.83, 1.05)	0.260	1.01 (0.96, 1.06)	0.708
Allergic rhinitis							
No. of cases = 4630	Model1	1.00 (0.97, 1.04)	0.800	0.83 (0.70, 0.98)	0.028	0.98 (0.92, 1.05)	0.569
	Model2	1.01 (0.98, 1.06)	0.467	0.82 (0.68, 0.97)	0.024	0.98 (0.92, 1.05)	0.593
	Model3	1.02 (0.98, 1.06)	0.455	0.82 (0.68, 0.98)	0.026	0.98 (0.92, 1.05)	0.639
Any allergic diseases							
No. of cases = 26,238	Model1	1.01 (1.00, 1.03)	0.077	0.86 (0.81, 0.92)	<0.001	1.00 (0.98, 1.03)	0.790
	Model2	1.02 (1.01, 1.04)	0.003	0.84 (0.79, 0.89)	<0.001	1.01 (0.98, 1.03)	0.536
	Model3	1.01 (0.99, 1.02)	0.256	0.85 (0.80, 0.91)	<0.001	1.00 (0.98, 1.03)	0.807

Model 1: Adjusted for maternal age and area of residence.
Model 2: Adjusted further for maternal blood mercury, selenium, or manganese concentration, and gestational week at sampling.
Model 3: Adjusted further for fish intake, pre-pregnancy BMI, smoking habit, alcohol intake, education level, household income, marital status, employment status, history of allergic diseases, parity, gestational duration, and infant sex.
Log2-transformed values of metallic element concentrations were used for multivariable modified Poisson regression models.

Table 4
Cumulative incidence ratios (CIRs) and 95% confidence intervals (CIs) of atopic dermatitis, food allergies, asthma, allergic rhinitis, and any allergic diseases according to quintiles of maternal blood concentrations of mercury, selenium, and manganese.

		Maternal blood mercury concentrations during pregnancy, ng/g, Median (IQR)					
		Q1: 1.8 (0.6)	Q2: 2.8 (0.4)	Q3: 3.6 (0.5)	Q4: 4.8 (0.7)	Q5: 7.2 (2.5)	*P* for trend [a]
	No. at risk	19,028	18,792	19,140	18,904	18,930	
Atopic dermatitis	No. of cases	1965	1957	1927	1883	1983	
	Adjusted-CIR (95%CI)	1.00	1.01 (0.95, 1.07)	0.99 (0.93, 1.05)	0.98 (0.92, 1.05)	1.05 (0.98, 1.12)	0.194
Food allergies	No. of cases	2184	2185	2179	2246	2103	
	Adjusted-CIR (95%CI)	1.00	0.98 (0.93, 1.04)	0.96 (0.91, 1.02)	1.01 (0.95, 1.07)	0.98 (0.92, 1.04)	0.902
Asthma	No. of cases	2009	1911	1976	1925	2036	
	Adjusted-CIR (95%CI)	1.00	0.97 (0.91, 1.03)	0.99 (0.93, 1.05)	0.98 (0.92, 1.04)	1.04 (0.98, 1.11)	0.092
Allergic rhinitis	No. of cases	985	869	909	932	935	
	Adjusted-CIR (95%CI)	1.00	0.91 (0.83, 0.99)	0.94 (0.86, 1.03)	0.97 (0.89, 1.07)	0.98 (0.9, 1.08)	0.585
Any allergic diseases	No. of cases	5360	5173	5234	5201	5270	
	Adjusted-CIR (95%CI)	1.00	0.97 (0.94, 1.00)	0.97 (0.94, 1.00)	0.98 (0.95, 1.02)	1.01 (0.98, 1.05)	0.182
	Maternal blood selenium concentrations during pregnancy, ng/g, Median (IQR)						
		Q1: 147.0 (9.0)	Q2: 159.0 (5.0)	Q3: 168.0 (5.0)	Q4: 179.0 (6.0)	Q5: 196.0 (15.0)	
	No. at risk	18,631	18,854	20,002	18,479	18,828	
Atopic dermatitis	No. of cases	2026	2036	2071	1857	1725	
	Adjusted-CIR (95%CI)	1.00	1.01 (0.96, 1.07)	0.98 (0.92, 1.04)	0.95 (0.89, 1.01)	0.87 (0.82, 0.93)	<0.001
Food allergies	No. of cases	2283	2252	2251	2152	1959	
	Adjusted-CIR (95%CI)	1.00	0.97 (0.92, 1.03)	0.93 (0.88, 0.99)	0.97 (0.92, 1.03)	0.89 (0.84, 0.95)	<0.001
Asthma	No. of cases	1960	2012	1994	1956	1935	
	Adjusted-CIR (95%CI)	1.00	1.01 (0.95, 1.07)	0.96 (0.90, 1.02)	0.99 (0.94, 1.05)	0.97 (0.91, 1.03)	0.241
Allergic rhinitis	No. of cases	964	936	961	924	845	
	Adjusted-CIR (95%CI)	1.00	0.98 (0.9, 1.07)	0.96 (0.88, 1.05)	0.99 (0.90, 1.08)	0.90 (0.82, 0.99)	0.043
Any allergic diseases	No. of cases	5391	5378	5442	5111	4916	
	Adjusted-CIR (95%CI)	1.00	0.99 (0.96, 1.02)	0.96 (0.93, 0.99)	0.97 (0.94, 1.00)	0.93 (0.89, 0.96)	<0.001
	Maternal blood manganese concentrations during pregnancy, ng/g, Median (IQR)						
		Q1: 10.6 (1.9)	Q2: 13.2 (1.1)	Q3: 15.4 (1.1)	Q4: 17.9 (1.5)	Q5: 22.1 (3.7)	
	No. at risk	19,297	18,521	19,212	18,770	18,994	
Atopic dermatitis	No. of cases	1980	1924	1981	1911	1919	
	Adjusted-CIR (95%CI)	1.00	1.02 (0.96, 1.08)	1.02 (0.96, 1.08)	1.02 (0.96, 1.09)	1.03 (0.97, 1.09)	0.423
Food allergies	No. of cases	2310	2109	2235	2127	2116	
	Adjusted-CIR (95%CI)	1.00	0.97 (0.92, 1.03)	1.02 (0.96, 1.07)	1.01 (0.95, 1.07)	1.01 (0.96, 1.07)	0.415
Asthma	No. of cases	1996	1860	1974	1987	2040	
	Adjusted-CIR (95%CI)	1.00	0.97 (0.92, 1.03)	0.98 (0.93, 1.04)	1.01 (0.96, 1.08)	1.02 (0.96, 1.08)	0.201
Allergic rhinitis	No. of cases	984	892	932	918	904	
	Adjusted-CIR (95%CI)	1.00	0.96 (0.88, 1.05)	0.96 (0.88, 1.05)	0.99 (0.90, 1.08)	0.97 (0.88, 1.06)	0.702
Any allergic diseases	No. of cases	5420	5089	5311	5204	5214	
	Adjusted-CIR (95%CI)	1.00	0.99 (0.96, 1.02)	1.00 (0.97, 1.03)	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)	0.314

Adjusted for maternal age, area of residence, the maternal blood mercury, selenium, or manganese concentration, gestational week at blood sampling, fish intake, pre-pregnancy BMI, smoking habit, alcohol intake, education level, household income, marital status, employment status, history of allergic diseases, parity, gestational duration, and infant sex.

[a] A test of linear trend was performed for median maternal blood metallic element concentrations ordered by quintile.

associations were consistently observed independent of infant sex, maternal age, and maternal history of allergic diseases. The associations between selenium exposure and risk were more evident for the lower mercury exposures.

The inverse associations between prenatal selenium concentrations and the risk of atopic dermatitis in the present study were consistent with the result of a previous cohort study of 834 Japanese mother-infant pairs but not with the result of UK cohort studies of approximately 2,000 mother-infant pairs, which found no association (Devereux et al., 2007; Shaheen et al., 2004). Selenium intake in Japan is higher than in Europe (100 μ/day vs. 50 μ/day) (Rayman, 2012; Yoshida, 1992). The median maternal blood selenium concentration in this study was 168 ng/g (μg/kg), which was higher than the 70–80 μg/kg in previous European studies (Devereux et al., 2007; Navarro et al., 1995).

A Polish study of 134 food-allergic children aged 1–36 months reported that children with food allergies had lower serum concentrations of selenium and zinc than those without them (Kamer et al., 2012). The present study added prospective evidence on an inverse association between prenatal selenium exposure and the risks of food allergies. The lack of association between selenium exposure and the risk of asthma was consistent with previous studies (Baïz et al., 2017; Devereux et al., 2007; Nurmatov et al., 2011), probably due to the observation period until three years of age when asthma was primarily non-atopic wheeze (Stein et al., 1997), and atopic asthma appears after six years of age (Saunes et al., 2012). In the EDEN birth cohort, a study of 861 mothers showed no association between maternal selenium and allergic rhinitis in children aged one and three years (Baïz et al., 2017). Our study added robust evidence with a larger number of cases of allergic rhinitis at three years of age. We found no associations between prenatal manganese exposures and risks of allergic diseases, which was not consistent with the results of previous studies (Pesce et al., 2021). There are reports of an increased risk of allergy with low manganese intake (Patel et al., 2006; Soutar et al., 1997), and the association is inconsistent. This study provides additional support for the controversy regarding the association of manganese with allergic diseases.

Our analysis suggests that maternal blood mercury concentration modifies the association between prenatal selenium exposure and the risk of atopic dermatitis and food allergies in early childhood. Again inverse associations were more pronounced for the lower mercury exposures. An underlying biological mechanism for the interaction between mercury and selenium exposure is the formation of Hg-Se complexes, which inhibit the activity of selenium-containing proteins, such as glutathione peroxidase, thereby increasing oxidative stress and inflammation (Carvalho et al., 2008; Reeves and Hoffmann, 2009). A previous *meta*-analysis showed no association between maternal fish intake during pregnancy and atopic outcomes in children (Beckhaus et al., 2015), although high tissue mercury concentrations in large, long-lived predatory fish suggest that pregnant or potentially pregnant

Table 5
Cumulative incidence ratios (CIRs) and 95% confidence intervals (CIs) atopic dermatitis, food allergies, asthma, allergic rhinitis, and any allergic diseases according to tertiles of maternal blood concentrations of mercury, selenium, and manganese, stratified by the tertiles of blood mercury concentrations.

		Tertiles of maternal blood selenium concentrations during pregnancy, ng/g, Median (IQR)				
Tertiles of maternal blood mercury concentrations, ng/g, Median (IQR)		T1: 152.0 (11.0)	T2: 168.0 (8.0)	T3: 188.0 (16.0)	*P* for trend [a]	*P* for interaction [b]
Atopic dermatitis						
	No. of cases / No. at risks	1576 / 14,317	1012 / 9931	676 / 7348		
	Maternal blood mercury T1: 2.2 (0.8)	1.00	0.95 (0.88, 1.03)	0.88 (0.81, 0.96)	0.005	
	No. of cases / No. at risks	1131 / 10,709	1173 / 11,086	861 / 9757		
	Maternal blood mercury T2: 3.6 (0.8)	1.00	1.02 (0.95, 1.10)	0.87 (0.80, 0.95)	0.001	0.216
	No. of cases / No. at risks	709 / 6392	1094 / 10,487	1483 / 14,753		
	Maternal blood mercury T3: 6.1 (2.4)	1.00	0.95 (0.87, 1.04)	0.92 (0.84, 1.00)	0.055	
Food allergies						
	No. of cases / No. at risks	1775 / 14,317	1092 / 9931	747 / 7348		
	Maternal blood mercury T1: 2.2 (0.8)	1.00	0.91 (0.84, 0.97)	0.87 (0.80, 0.94)	<0.001	
	No. of cases / No. at risks	1272 / 10,709	1269 / 11,086	1115 / 9757		
	Maternal blood mercury T2: 3.6 (0.8)	1.00	0.98 (0.91, 1.05)	1.00 (0.92, 1.08)	0.944	0.246
	No. of cases / No. at risks	793 / 6392	1208 / 10,487	1626 / 14,753		
	Maternal blood mercury T3: 6.1 (2.4)	1.00	0.93 (0.86, 1.02)	0.91 (0.84, 0.98)	0.028	
Asthma						
	No. of cases / No. at risks	1534 / 14,317	1038 / 9931	728 / 7348		
	Maternal blood mercury T1: 2.2 (0.8)	1.00	0.97 (0.90, 1.05)	0.92 (0.85, 1.00)	0.067	
	No. of cases / No. at risks	1129 / 10,709	1082 / 11,086	1005 / 9757		
	Maternal blood mercury T2: 3.6 (0.8)	1.00	0.94 (0.87, 1.01)	0.98 (0.90, 1.06)	0.621	0.056
	No. of cases / No. at risks	687 / 6392	1043 / 10,487	1611 / 14,753		
	Maternal blood mercury T3: 6.1 (2.4)	1.00	0.94 (0.86, 1.03)	1.01 (0.93, 1.10)	0.372	
Allergic rhinitis						
	No. of cases / No. at risks	738 / 14,317	477 / 9934	345 / 7349		
	Maternal blood mercury T1: 2.2 (0.8)	1.00	0.95 (0.85, 1.07)	0.96 (0.84, 1.09)	0.428	
	No. of cases / No. at risks	537 / 10,709	510 / 11,089	450 / 9759		
	Maternal blood mercury T2: 3.6 (0.8)	1.00	0.95 (0.84, 1.07)	0.96 (0.85, 1.09)	0.559	0.978
	No. of cases / No. at risks	321 / 6392	546 / 10,488	706 / 14,757		
	Maternal blood mercury T3: 6.1 (2.4)	1.00	1.05 (0.92, 1.20)	0.95 (0.84, 1.09)	0.244	
Any allergic diseases						
	No. of cases / No. at risks	4188 / 14,317	2734 / 9934	1888 / 7349		
	Maternal blood mercury T1: 2.2 (0.8)	1.00	0.96 (0.92, 1.00)	0.91 (0.87, 0.95)	<0.001	
	No. of cases / No. at risks	3004 / 10,709	2988 / 11,089	2603 / 9759		
	Maternal blood mercury T2: 3.6 (0.8)	1.00	0.98 (0.93, 1.02)	0.98 (0.93, 1.02)	0.320	0.015
	No. of cases / No. at risks	1859 / 6392	2889 / 10,488	4085 / 14,757		
	Maternal blood mercury T3: 6.1 (2.4)	1.00	0.96 (0.91, 1.01)	0.96 (0.92, 1.01)	0.180	

Adjusted for maternal age, area of residence, the maternal blood mercury, selenium, or manganese concentration, gestational week at blood sampling, fish intake, pre-pregnancy BMI, smoking habit, alcohol intake, education level, household income, marital status, employment status, history of allergic diseases, parity, gestational duration, and infant sex.
IQR: Interquartile range.
[a] A test for a linear trend in incidence ratios stratified by prenatal mercury exposures, ordering the median of maternal blood selenium concentrations in each tertile, was used.
[b] Interaction terms: The median of tertiles of blood selenium concentration was multiplied by the median of tertiles of blood mercury concentration.

women should limit the consumption of golden bass, shark, swordfish, king mackerel, white tuna, and so on, to minimize mercury exposure (Mozaffarian and Rimm, 2006).

The potential biological mechanisms underlying metallic element exposure to allergic diseases in children generally involve oxidative stress, which is linked to the immune system (Chang et al., 2016; Ozsurekci and Aykac, 2016; Sultana et al., 2017; Wei Choo et al., 2021). Previous studies have shown that toxic elements, such as mercury, cadmium, nickel, and arsenic, were associated with increased oxidative stress (Farina et al., 2011; Valko et al., 2005). Furthermore, cord blood from infants prenatally exposed to methylmercury via maternal seafood consumption had decreased numbers of the naive helper T-cell subset CD4+/CD45RA + and IgM levels compared with infants with lower prenatal exposure (Belles-Isles et al., 2002). In contrast, selenium and manganese are essential trace elements with antioxidant and anti-inflammatory properties (Hariharan and Dharmaraj, 2020; Patel et al., 2006; Vunta et al., 2007). Inflammation in the dermis, a hallmark of atopic dermatitis, may be enhanced by oxidative stress through the activation of the nuclear factor kappa B (NF-κB) pathway inducing the expression of pro-inflammatory cytokines such as IL-6, IL-8, IL-9, and IL-33 (Kruk and Duchnik, 2014; Wullaert et al., 2011; Yao et al., 2011). Selenium works as a component of antioxidative enzymes and can protect the organism from oxidative stress (Tapiero et al., 2003).

This study provided evidence linking prenatal metallic element exposure to the development of allergic diseases after birth. The strengths of this study included a large-scale birth cohort study around Japan, which may be representative of general Japanese pregnant women, and the quantitative assessment of maternal blood metallic element concentrations. As for a limitation, there were unmeasured and residual confounding factors, although we adjusted for many potential confounding variables.

Our study findings suggest that the intake of selenium-rich food for pregnant women may prevent allergic diseases in children. Also, consumption of large, long-lived predatory fish potentially rich in mercury should be limited to enhance the beneficial effect of selenium.

5. Conclusion

Prenatal selenium exposure was associated with lower risks of atopic dermatitis and food allergies but not with asthma, in early childhood until three years of age, while mercury or manganese exposure was not associated with the risk. The inverse associations by selenium exposure

were more evident for lower mercury exposures. Our findings suggest that prenatal exposure to selenium may be beneficial for reducing the risk of allergic diseases in early childhood.

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Ethics issues

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions (Ethical Number: No.100910001). The JECS was conducted in accordance with the Declaration of Helsinki and other nationally valid regulations and guidelines. Participant recruitment involved a face-to-face explanation of the survey to mothers and written informed consent was obtained and recorded from all participants.

CRediT authorship contribution statement

Junji Miyazaki: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Satoyo Ikehara:** Investigation, Data curation, Writing – review & editing, Supervision. **Kanami Tanigawa:** Formal analysis, Writing – review & editing. **Takashi Kimura:** Formal analysis, Writing – review & editing. **Kimiko Ueda:** Writing – review & editing. **Keiichi Ozono:** Writing – review & editing. **Tadashi Kimura:** Writing – review & editing. **Yayoi Kobayashi:** Writing – review & editing, Validation, Project administration. **Shin Yamazaki:** Writing – review & editing, Validation, Project administration, Funding acquisition. **Michihiro Kamijima:** Writing – review & editing, Project administration. **Tomotaka Sobue:** Writing – review & editing, Supervision, Project administration. **Hiroyasu Iso:** Investigation, Writing – review & editing, Supervision, Project administration.

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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Appendix A

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Appendix B. Supplementary material

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