

Association between blood levels of PCDDs/PCDFs/dioxin-like PCBs and history of allergic and other diseases in the Japanese population

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Abstract

Background Previous studies reported that exposure to dioxins was associated with an increased risk of various diseases in general populations.

Objectives The aim of this study was to examine the association between levels of dioxins in blood and allergic and other diseases.

Methods We conducted a cross-sectional study on 1,063 men and 1,201 women (aged 15–76 years), who were living throughout Japan and not occupationally exposed to dioxins, during 2002–2010. In fasting blood samples, polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like PCBs (DL-PCBs) were analyzed by isotope dilution high-resolution gas chromatography/mass spectrometry. We obtained information on life style and self-reported history of diseases using a questionnaire. Blood pressure, blood

levels of hemoglobin A1c, and serum lipids were also measured. Multiple logistic regression models were used to analyze the association between dioxin levels in blood and various diseases.

Results Toxic equivalents of PCDDs/PCDFs and total dioxins showed significant inverse dose–response relationships with atopic dermatitis, after adjustments for potential confounders. The highest quartile for total dioxins had an adjusted odds ratio of 0.26 (95 % confidence interval 0.08–0.70) compared to the reference group (first quartile). The odds ratios for hypertension, diabetes mellitus, hyperlipidemia, gout in men, and gynecologic diseases in women significantly increased with increasing toxic equivalents of PCDDs/PCDFs, DL-PCBs, and total dioxins in blood.

Conclusions The present findings suggest that background exposure to dioxins was associated with reduced risk of atopic dermatitis. The results also support the idea that low-level exposure to dioxins is associated with an increased risk of diabetes, hypertension, and hyperlipidemia.

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Introduction

Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzo-furans (PCDFs) are a group of chemical substances described as persistent organic pollutants (POPs). They are generated unintentionally during the combustion of materials containing chlorine (WHO/IARC 1997). PCDDs/PCDFs exhibit various biological and toxic actions, such as dermal toxicity, immune toxicity, hepatotoxicity, carcinogenicity, and adverse effects on

reproductive, neurobehavioral, and endocrine functions (Lindström et al. 1995; Weisglas-Kuperus 1998). Polychlorinated biphenyls (PCBs) were produced for various industrial purposes, such as dielectric fluids in transformers and capacitors, from the 1930s to 1970s. PCBs are also detected ubiquitously in nature, although their production and use were banned in the 1970s. Some PCB congeners (12 non-ortho- and mono-ortho-PCBs) are known to exhibit toxic actions similar to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and are called dioxin-like PCBs (DL-PCBs) (van den Berg et al. 2006).

Studies have found a relationship between heavy exposure to dioxins and diseases such as diabetes mellitus (Henriksen et al. 1997), hypertension (Wang et al. 2008), hyperlipidemia (Hirota et al. 1993; Calvert et al. 1996), and endometriosis (Eskenazi et al. 2002). Recently, it has been reported that low-level exposure to dioxins may also be associated with these health problems in general populations (Arisawa et al. 2005; Lee et al. 2006; Ha et al. 2009; Uemura et al. 2009; Porpora et al. 2009).

In the past several decades, the morbidity rate for allergic diseases has increased, chiefly in developed countries (Laughter et al. 2000; Wahn and von Mutius 2001). Allergic diseases clinically include hay fever, allergic rhinitis, asthma, atopic dermatitis, and food allergy, in which IgE-associated immune responses are directed against innocuous environmental protein antigens (Biedermann and Röcken 1999). In previous studies on mice or humans, a helper T (Th2)-dominated immune balance has been identified as the chief cause of allergic diseases (Ngoc et al. 2005). Interleukin (IL)-4- and IL-13-producing Th2 cells are involved in allergic reactions such as increased IgE production by B lymphocytes, high frequency of FcγRI + antigen-presenting cells (APC), or the chronic allergic inflammation of asthma and atopic dermatitis, directly or indirectly (Biedermann and Röcken 1999). However, environmental and genetic risk factors, and the mechanism of allergic diseases have not been fully clarified.

It remains unclear whether environmental exposure to dioxins decreases or increases the morbidity rates for allergic diseases. In NC/Nga mice, known as an atopic model, TCDD exposure reduced anti-OVA and total IgE production and prevented the development of atopic diseases-like skin lesions (Fujimaki et al. 2002). On the other hand, exposure to TCDD exacerbated atopic diseases with no increase in IgE production in NC/Nga mice (Ito et al. 2008). In Dutch preschool children, an association between body burden of PCBs and a lower risk of allergic reactions was reported (Weisglas-Kuperus et al. 2000).

In Japan, “A Survey on the Accumulation of Dioxins and Other Chemical Compounds in Humans” has been performed under the supervision of the Ministry of the Environment of Japan since 2002. The purpose of this

project was to clarify the body burden and the dietary intake of dioxins and other POPs, and their related factors in the Japanese population (Uemura et al. 2009). Accumulated data on over 2,000 subjects enabled us to extensively analyze the association between dioxin levels in blood and a history of allergic and other diseases.

Subjects and methods

Study population

The present study population consisted of 2,266 subjects (1,063 men and 1,203 women) aged 15–76 years, who were living in 125 different areas of 45 prefectures in Japan. The recruitment of the participants was done in urban areas, farming villages and fishing villages of each prefecture between 2002 and 2008, and in urban areas and either farming village or fishing village of each prefecture in 2009 and 2010. The eligibility criteria were to have been living in the respective residential area for at least 10 years, to not frequently leave the study area for work or other reasons, to have had no occupational exposure to PCDDs, PCDFs or DL-PCBs, and to have no severe anemia or other health problems that interfere with blood collection. The open call for participants was performed by public relations magazine, a poster, a website by a local government office, and broadcast in the area. In this study, the participation was essentially voluntary, and after explaining the details of the study, we obtained written informed consent from each participant. We designed the study to recruit at least 250 participants every survey year from 2002 to 2008. The number of study subjects was reduced in 2009 and 2010 because of financial constraints. A few subjects were excluded because of severe anemia or other health problems during the survey years. Two subjects were excluded due to missing values for blood levels of dioxins, leaving 2,264 persons for analysis. The study protocol was reviewed and approved by the Ethical Committee of the Ministry of the Environment, Government of Japan.

Measurement of blood pressure and collection and analysis of blood samples

Approximately 20–30 ml of fasting venous blood was obtained from each participant, and 20 ml was collected into a vacutainer tube containing a sodium heparin solution (VT-100H, Terumo, Tokyo, Japan or 367677, Becton, Dickson and Company, Tokyo, Japan) for analysis of dioxins. Blood levels of PCDDs, PCDFs, and DL-PCBs were measured using high-resolution gas chromatography/mass spectrometry after liquid/liquid extraction and gel clean-up, at the Institute of General Science for the

Environment, IDEA Consultants, Inc., Yaizu, Shizuoka, Japan. The analytical procedure has been reported previously (Arisawa et al. 2003; Nakamura et al. 2008).

Blood lipids (%) were measured gravimetrically using the sulfuric ammonium–ethanol/hexane technique, and the levels of dioxins in blood were expressed as a function of blood lipids. The limit of detection was 1 pg/g lipid for PCDDs/PCDFs with four or five chlorine atoms, 2 pg/g lipid for PCDDs/PCDFs with six or seven chlorine atoms, 4 pg/g lipid for OctaCDD/OctaCDF, and 10 pg/g lipid for DL-PCBs. Calculations of toxic equivalents (TEQ) were based on toxicity equivalency factors of WHO 2005 (van den Berg et al. 2006). If the level of the pollutant was below the limit of detection, a value of zero was assigned.

Blood pressure was measured in each study subject sitting at rest. When a measurement was extremely high or low, or far from usual value of each participant, we repeated measurement again after a short rest.

Levels of hemoglobin A1c in blood, and total cholesterol, triglyceride, docosahexaenoic acid (DHA), di-homo- γ -linolenic acid (GLA), and arachidonic acid (AA) in serum were also measured.

Questionnaire

The participants were requested to complete a questionnaire to obtain data on individual characteristics, including body height and weight, past history of diseases and treatments, residential and occupational histories, smoking habits, and frequency of food intake. Regarding information on past history of diseases and treatments, the participants were asked whether they had been diagnosed with any of 20 diseases by physicians. In the present study, the analysis was restricted to 12 diseases, after excluding nine diseases with less than 30 patients (stroke, coronary heart disease, emphysema, chronic liver disease, liver cirrhosis, liver cancer, gastric cancer, lung cancer, colon cancer).

Subjects who had a history of physician-diagnosed hypertension, or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg were defined as having hypertension, and those who had a history of diabetes or blood levels of HbA1c > 6.1 % were defined as having diabetes. In addition, persons who had a history of hyperlipidemia, or serum levels of total cholesterol levels ≥ 220 mg/dl or serum triglyceride levels ≥ 150 mg/dl were regarded as having hyperlipidemia.

Frequency of intake of foods/food groups was classified into the following five categories: almost every day (6 times/week), 3–4 times/week (3.5/week), 1–2 times/week (1.5/week), 1–2 times/month (0.35/week), and almost never (0.1/week). We did not specify the unit or portion of each item. Fish and shellfish included seven items: coastal

fish such as horse mackerel, mackerel, and sardine; other fish such as tuna, salmon, and bonito; cuttlefish and octopus; crab; shrimp; tubular roll of grilled fish paste; and short-neck clam and corbicula. The frequency of intake of fish and shellfish was calculated by summing the intake frequencies of seven items. Regarding drinking habits, subjects were asked how often they had consumed beer, rice wine (sake), and distilled spirits over the previous month. The frequency of alcohol consumption was calculated as the sum of the frequency of each item, and then divided into three categories: regular, ≥ 3 times/week; often, $1 < 3$ times/week; rarely or never, < 1 times/week. Smoking habit was classified into three categories: current smokers, smokers who quit smoking, and never smokers. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared.

Statistical analysis

Simple linear regression, two-sample *t* test, one-way analysis of variance, and Scheffé's multiple-comparisons procedure were used to examine the associations of the blood levels of dioxins with age, sex, BMI, regional block, residential area, survey year, and smoking and drinking habits, depending on the type of variable (continuous or categorical) and the number of groups (two or more than two groups). Associations between the accumulated TEQs of dioxins and the history of allergic and other diseases were examined using multiple logistic regression models, adjusted for age, sex, regional block, survey year, and smoking and drinking habits. In the analysis of hypertension, diabetes, hyperlipidemia, and gout, BMI was considered as a potential confounder, and additionally adjusted. Previous epidemiologic studies suggested that intake of ω -6 polyunsaturated fatty acids increases the risk, while intake of fish and ω -3 fatty acids decreases the risk for allergic diseases (Kremmyda et al. 2011). Therefore, in the analysis of atopic dermatitis, serum levels of ω -3 and ω -6 fatty acids, and frequency of food intake were considered as potential confounders, and further adjusted in separate models. The accumulated TEQs of PCDDs/PCDFs, DL-PCBs, and total dioxins were divided into quartiles, and the first quartile was defined as the reference. Dummy variables were created for PCDDs/PCDFs, DL-PCBs, total dioxins, sex, age, BMI, drinking habit, smoking habit, regional block, survey year, consumption of fish, meat, and dairy products, DHA, GLA, AA, and those except for reference categories were included in the model. Odds ratio (OR) and profile likelihood confidence intervals (CI) were presented. We conducted tests of trends using the median value for each quartile of the TEQs in logistic models. Likelihood ratio tests were performed in this analysis.

P values <0.05 in two-tailed test were considered significant. All statistical analyses used the SAS software package (version 8.2, SAS Institute Inc. 1997).

Results

Study population and PCDDs, PCDFs, DL-PCBs, and total dioxins in blood

Table 1 shows the characteristics of the participants. Of the 2,264 subjects, 1,063 (47.0 %) were men and 1,201 (53.0 %) were women. The mean age $\pm$ SD was 43.5 ± 13.6 years in men and 45.3 ± 14.0 years in women. The mean $\pm$ SD of BMI was 23.8 ± 3.5 kg/m² and 22.3 ± 3.3 kg/m² in male and female subjects, respectively. The number of participants in each regional block was almost equivalent. Regarding the number of subjects according to residential area, the proportions for urban areas, farming villages, and fishing villages were 41.4, 29.8, and 28.8 %, respectively. The proportion of ex-smokers combined with current smokers was 62.4 % in men and 11.8 % in women. The proportion of habitual drinkers (≥ 1 day/week) was 65.0 % in men and 25.2 % in women.

The concentration and TEQ for each congener of PCDDs, PCDFs, and DL-PCBs in blood are presented in Table 2. The median TEQ of PCDDs, PCDFs, DL-PCBs, and total dioxins was 6.9, 2.8, 5.6, and 16 pgTEQ/g lipid, respectively. In the calculation of TEQ, the congeners contributing most were 1,2,3,7,8-PentaCDD, 2,3,4,7,8-PentaCDF, and PCB 126 for PCDDs, PCDFs, and DL-PCBs, respectively.

The TEQ of PCDDs/PCDFs, DL-PCBs, and total dioxins significantly increased with age ($P < 0.0001$). Blood levels of PCDDs/PCDFs and total TEQ did not differ according to sex, but the levels of DL-PCBs were significantly lower among women than among men ($P = 0.003$). BMI was positively correlated with blood levels of PCDDs/PCDFs, DL-PCBs, and total TEQ ($P < 0.0001$). There were significant differences in the blood levels of dioxins according to regional block ($P < 0.0001$), with TEQ of PCDDs/PCDFs and total TEQ being highest in the Chugoku/Shikoku region and with TEQ of DL-PCBs highest in the Kyushu/Okinawa region. The TEQ of PCDDs/PCDFs, DL-PCBs, and total dioxins were significantly higher in fishing villages than in urban area and farming villages ($P < 0.05$). Blood levels of PCDDs/PCDFs and total dioxins, but not DL-PCBs, significantly decreased with survey year ($P < 0.0001$). With regard to smoking habit, TEQ of DL-PCBs and total dioxins were significantly higher among ex-smokers than among current and non-smokers ($P < 0.05$). Regular drinkers had significantly higher blood levels of DL-PCBs and total dioxins than

Table 1 Characteristics of the participants

	Men No. (%)	Women No. (%)
Participants	1,063 (47.0)	1,201 (53.0)
Age (years)		
15–19	32 (3.0)	39 (3.2)
20–29	172 (16.2)	161 (13.4)
30–39	234 (22.0)	217 (18.1)
40–49	228 (21.4)	268 (22.3)
50–59	265 (24.9)	301 (25.1)
60–69	125 (11.8)	206 (17.2)
70–76	7 (0.7)	9 (0.7)
BMI category (kg/m ²)		
<18.5	30 (2.8)	118 (9.8)
≥ 18.5 and <25	682 (64.2)	858 (71.4)
≥ 25	341 (32.1)	215 (17.9)
Unknown	10 (0.9)	10 (0.8)
Regional block		
Hokkaido/Tohoku	193 (18.2)	258 (21.5)
Kanto/Koshin'etsu	202 (19.0)	246 (20.5)
Tokai/Hokuriku/Kinki	248 (23.3)	217 (18.1)
Chugoku/Shikoku	214 (20.1)	229 (19.1)
Kyushu/Okinawa	206 (19.4)	251 (20.9)
Residential area		
Urban	431 (40.5)	507 (42.2)
Farming village	314 (29.5)	361 (30.1)
Fishing village	318 (29.9)	333 (27.7)
Survey year		
2002	117 (11.0)	142 (11.8)
2003	123 (11.6)	149 (12.4)
2004	112 (10.5)	152 (12.7)
2005	135 (12.7)	153 (12.7)
2006	140 (13.2)	151 (12.6)
2007	128 (12.0)	154 (12.8)
2008	129 (12.1)	127 (10.6)
2009	76 (7.1)	102 (8.5)
2010	103 (9.7)	71 (5.9)
Smoking habit		
Current	399 (37.5)	75 (6.2)
Ever	264 (24.8)	67 (5.6)
Never	398 (37.4)	1,050 (87.4)
Unknown	2 (0.2)	9 (0.7)
Drinking habit		
Regular (≥ 3 days/week)	560 (52.7)	177 (14.7)
Often (1–3 days/week)	131 (12.3)	126 (10.5)
Rarely (<1 day/week)	342 (32.2)	858 (71.4)
Unknown	30 (2.8)	40 (3.3)

those who drank often or rarely ($P < 0.05$), and significantly higher levels of PCDDs/PCDFs than those who drank rarely ($P < 0.05$) (data not shown).

Table 2 The concentration and TEQ for each congener of PCDDs/PCDFs and DL-PCBs in blood ($N = 2,264$)

Congeners	Concentration (pg/g lipid)					TEQ (pg/g lipid)				
	5 %	25 %	50 %	75 %	95 %	5 %	25 %	50 %	75 %	95 %
2,3,7,8-TeCDD	0	0	1	2	3	0.0	0.0	1.0	2.0	3.0
1,2,3,7,8-PeCDD	2	3	4	6	11	2.0	3.0	4.0	6.0	11
1,2,3,4,7,8-HxCDD	0	0	0	3	4	0.0	0.0	0.0	0.3	0.4
1,2,3,6,7,8-HxCDD	4	9	13	21	39	0.4	0.88	1.3	2.1	3.9
1,2,3,7,8,9-HxCDD	0	0	3	4	7	0.0	0.0	0.3	0.4	0.7
1,2,3,4,6,7,8-HpCDD	5	8	11	17	34	0.05	0.08	0.11	0.17	0.34
OCDD	54	89	130	220	680	0.02	0.03	0.04	0.07	0.2
2,3,7,8-TeCDF	0	0	0	1	3	0.0	0.0	0.0	0.1	0.3
1,2,3,7,8-PeCDF	0	0	0	0	2	0.0	0.0	0.0	0.0	0.06
2,3,4,7,8-PeCDF	3	5	7	11	19	0.9	1.5	2.1	3.3	5.7
1,2,3,4,7,8-HxCDF	0	0	2	4	6	0.0	0.0	0.2	0.4	0.6
1,2,3,6,7,8-HxCDF	0	2	3	5	8	0.0	0.2	0.3	0.5	0.8
1,2,3,7,8,9-HxCDF	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0
2,3,4,6,7,8-HxCDF	0	0	0	2	4	0.0	0.0	0.0	0.2	0.4
1,2,3,4,6,7,8-HpCDF	0	0	2	3	6	0.0	0.0	0.02	0.03	0.06
1,2,3,4,7,8,9-HpCDF	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0
OCDF	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0
PCB 77	0	0	0	0	20	0.0	0.0	0.0	0.0	0.0
PCB 81	0	0	0	0	0	0.0	0.0	0.0	0.0	0.0
PCB 126	10	20	40	80	170	1.0	2.0	4.0	8.0	17
PCB 169	10	20	30	50	100	0.3	0.6	0.9	1.5	3.0
Non-orthos						1.3	2.9	5.2	9.4	20
PCB 105	360	740	1,300	2,300	5,100	0.01	0.02	0.04	0.07	0.15
PCB 114	110	250	470	885	1,900	0.0	0.01	0.01	0.03	0.06
PCB 118	2,000	4,100	7,400	13,000	28,000	0.06	0.12	0.22	0.39	0.84
PCB 123	30	60	100	190	440	0.0	0.00	0.00	0.01	0.01
PCB 156	670	1,500	2,800	4,900	9,700	0.02	0.05	0.08	0.15	0.29
PCB 157	200	420	770	1,300	2,700	0.01	0.01	0.02	0.04	0.08
PCB 167	360	730	1,300	2,300	4,700	0.01	0.02	0.04	0.07	0.14
PCB 189	90	180	330	570	1,100	0.0	0.01	0.01	0.02	0.03
Mono-ortho PCBs						0.12	0.25	0.44	0.78	1.6
Total PCDDs						2.5	4.1	6.9	11	18
Total PCDFs						0.9	1.8	2.8	4.4	7.7
Total (PCDDs/PCDFs)						3.3	6.1	9.8	15	26
Total DL-PCBs						1.4	3.2	5.6	10	21
Total TEQ						4.8	9.7	16	25	45

Values below the detection limit were replaced with 0

TEQ values were based on WHO-TEF (van den Berg et al. 2006)

History of allergy and other diseases

Table 3 presents the number of persons who had a history of allergic and other diseases. There were 380 subjects with allergic rhinitis, 118 with atopic dermatitis, and 93 subjects with asthma. Except for allergic diseases, the most frequent disease was hyperlipidemia ($N = 986$), followed by hypertension ($N = 647$), gastric ulcer ($N = 196$), diabetes mellitus ($N = 114$), and thyroid diseases ($N = 73$).

In women, there were 161 subjects with a history of gynecological diseases.

Association between dioxins in blood and a history of disease

The multivariate-adjusted associations between blood levels of dioxins and the history of allergic and other diseases are presented in Table 4. TEQ of PCDDs/PCDFs and total

Table 3 Frequency of allergic and other diseases

	No. of cases in men No. (%)	No. of cases in women No. (%)
Asthma	40 (3.8)	53 (4.4)
Atopic dermatitis	40 (3.8)	78 (6.5)
Allergic rhinitis	127 (11.9)	253 (21.1)
Hypertension ^a	362 (34.1)	285 (23.8)
Diabetes mellitus ^b	73 (6.9)	41 (3.4)
Hyperlipidemia ^c	500 (47.1)	486 (40.5)
Gout	58 (5.5)	1 (0.1)
Thyroid diseases	10 (0.9)	63 (5.2)
Kidney disease	17 (1.6)	30 (2.5)
Gastric ulcer	119 (11.2)	77 (6.4)
Gynecological disease	0 (0.0)	161 (13.4)

^a History of hypertension or systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg

^b History of diabetes mellitus or hemoglobin A1c in blood >6.1 %

^c History of hyperlipidemia or serum total cholesterol ≥ 220 mg/dl or serum triglycerides ≥ 150 mg/dl

dioxins, but not of DL-PCBs, showed significant inverse dose–response relationships with atopic dermatitis. The adjusted ORs of atopic dermatitis across quartiles of total dioxins were 1.0, 0.86, 0.93, and 0.26 for total TEQ (P for trend = 0.02). There were significant positive dose–response relationships between the TEQ of PCDDs/PCDFs, DL-PCBs, and total TEQ, and a history of hypertension, diabetes mellitus, and hyperlipidemia. In addition, the TEQ of PCDDs/PCDFs, DL-PCBs, and total TEQ also showed significant positive trends with a history of gout in men and gynecologic diseases in women.

To assess the possibility of confounding by serum levels of ω -3 fatty acids or ω -6 fatty acids, or consumption of fish, meat, and dairy products, an analysis for atopic dermatitis was performed by additionally adjusting for the effects of these variables (Table 5). However, adjustments for serum fatty acid levels or food consumption did not substantially alter the results. In the adjusted models including fish consumption (Model 2) or serum levels of DHA (Model 3), P values for trends were 0.04 and 0.05, respectively, for total TEQ. In the adjusted models including serum levels of GLA (Model 4), AA (Model 5), meat consumption (Model 6), and dairy products consumption (Model 7) as covariates, all P values for trends were 0.02 for total TEQ. The ORs of atopic dermatitis in the highest quartile of total TEQ were significantly lower than the reference for all models (Model 2 to Model 7). On the other hand, serum levels of ω -3 or ω -6 fatty acids, or consumption of fish, meat, or dairy products were not significantly associated with atopic dermatitis in Models 2–7.

Discussion

The median of total TEQ in the blood of this study population for the nine survey years (2002–2010) was 16 pg TEQ/g lipid. This value was approximately 20 % lower than that of our previous report (Uemura et al. 2009), which used data from the surveys of 2002–2006 and the TEFs of WHO 1998. The blood levels of dioxins in the present study were similar to those recently reported for other populations in Japan (Todaka et al. 2011), Taiwan (Hsu et al. 2009), Korea (Park et al. 2010), Germany (Fromme et al. 2009), and the United States (Lorber et al. 2009).

The decreased OR of atopic dermatitis observed in this study was not at all unexpected. Among 207 Dutch children at the age of 42 months, prenatal exposure to PCB (PCB118 and three non-DL-PCBs) was associated with a significantly reduced risk of asthma-like symptoms, and current PCB exposure was associated with increased risks of recurrent otitis media and chicken pox and a decreased risk of allergic reactions (Weisglas-Kuperus et al. 2000). An association between prenatal PCB exposure and a reduced frequency of allergic diseases was also observed in a further follow-up study of 167 children of preschool age (Weisglas-Kuperus et al. 2004). ten Tusscher et al. (2003) also reported that prenatal and postnatal exposure to PCDDs/PCDFs was associated with a decreased risk of allergy in 27 children of the Netherlands aged 8 years. On the other hand, in a recent cohort study performed in Japan, though exposure to dioxins significantly affected otitis media, the OR of food allergy was significantly increased for non-ortho PCBs and mono-ortho PCBs, in 364 children aged 18 months (Miyashita et al. 2011). Overall, prospective cohort studies have showed that background exposure to PCBs/dioxins was associated with an increased risk of infectious diseases and a reduced risk of allergic diseases, despite some inconsistencies.

One explanation for the decreased risk of atopic dermatitis is that exposure to dioxins changes the immune balance, for example, enhancing Th1-type and suppressing Th2-type immune responses. This idea is supported by the observation that exposure to PCB/dioxins was associated with an increased risk of infectious diseases (Weisglas-Kuperus et al. 2000, 2004; Miyashita et al. 2011) and that microbial infection early in life leads to immune deviation from Th2- to Th1-type responses through the activation of regulatory T-cells (Palomares et al. 2010).

In experimental studies, Luebke et al. (2001) showed that TCDD exposure of Brown Norway rats before intra-tracheal sensitization with house dust mite allergen suppressed the development of allergic immune responses and antigen-specific IgE production. In NC/Nga mice (an atopic model), the production of Th2-type cytokines such

Table 4 Association between dioxins in blood and history of allergic and other diseases

	Cases/no. of subjects	Q1 (<25th) Reference	Q2 (25th to <50th) OR (95 % CI)	Q3 (50th to <75th) OR (95 % CI)	Q4 ($\geq$ 75th) OR (95 % CI)	P for trend
PCDDs/PCDFs^c						
Asthma ^a	93/2,253	1	0.78 (0.42–1.4)	1.1 (0.59–2.1)	1.2 (0.55–2.5)	0.48
Atopic dermatitis ^a	117/2,253	1	0.87 (0.53–1.4)	0.62 (0.32–1.2)	0.46 (0.18–1.0)	0.04
Allergic rhinitis ^a	379/2,253	1	1.3 (0.94–1.7)	1.0 (0.70–1.4)	0.70 (0.45–1.1)	0.04
Hypertension ^b	638/2,232	1	1.1 (0.81–1.6)	1.3 (0.91–1.9)	1.7 (1.2–2.6)	0.001
Diabetes mellitus ^b	113/2,216	1	6.8 (1.9–43)	6.8 (1.9–44)	10 (2.9–66)	0.002
Hyperlipidemia ^b	976/2,229	1	1.7 (1.3–2.3)	2.1 (1.6–2.9)	2.9 (2.1–4.0)	<0.0001
Gout (men) ^b	57/1,051	1	5.2 (1.4–34)	6.8 (1.7–46)	8.7 (2.1–60)	0.02
Thyroid diseases ^a	73/2,253	1	1.1 (0.49–2.5)	1.1 (0.48–2.6)	1.2 (0.49–2.9)	0.75
Kidney disease ^a	47/2,253	1	0.96 (0.36–2.6)	0.87 (0.32–2.5)	0.56 (0.19–1.7)	0.21
Gastric ulcer ^a	196/2,253	1	1.3 (0.79–2.2)	1.2 (0.70–2.0)	0.77 (0.44–1.4)	0.07
Gynecological disease ^a	161/1,192	1	1.2 (0.66–2.2)	2.1 (1.2–3.8)	2.0 (1.1–4.0)	0.03
DL-PCBs^d						
Asthma ^a	93/2,253	1	1.4 (0.77–2.4)	1.1 (0.54–2.2)	0.91 (0.38–2.1)	0.57
Atopic dermatitis ^a	117/2,253	1	1.2 (0.77–2.0)	1.0 (0.54–1.9)	0.44 (0.14–1.2)	0.12
Allergic rhinitis ^a	379/2,253	1	1.2 (0.88–1.6)	0.92 (0.63–1.3)	0.98 (0.63–1.5)	0.62
Hypertension ^b	638/2,232	1	1.5 (1.0–2.3)	1.6 (1.1–2.4)	2.4 (1.6–3.7)	<0.0001
Diabetes mellitus ^b	113/2,216	1	2.5 (0.61–17)	6.7 (1.8–44)	11 (3.0–76)	<0.0001
Hyperlipidemia ^b	976/2,229	1	1.8 (1.3–2.4)	2.7 (1.9–3.7)	3.8 (2.7–5.5)	<0.0001
Gout (men) ^b	57/1,051	1	1.6 (0.46–6.4)	1.9 (0.56–7.7)	3.3 (0.94–14)	0.04
Thyroid diseases ^a	73/2,253	1	1.7 (0.76–4.0)	0.72 (0.28–1.9)	0.84 (0.31–2.3)	0.24
Kidney disease ^a	47/2,253	1	0.43 (0.15–1.2)	0.44 (0.15–1.3)	0.53 (0.17–1.7)	0.90
Gastric ulcer ^a	196/2,253	1	0.94 (0.56–1.6)	0.80 (0.46–1.4)	0.72 (0.40–1.3)	0.22
Gynecological disease ^a	161/1,192	1	2.2 (1.2–4.3)	2.9 (1.5–5.9)	3.3 (1.6–7.3)	0.02
Total dioxins^e						
Asthma ^a	93/2,253	1	1.1 (0.64–2.0)	0.97 (0.48–1.9)	1.1 (0.49–2.4)	0.88
Atopic dermatitis ^a	117/2,253	1	0.86 (0.53–1.4)	0.93 (0.50–1.7)	0.26 (0.08–0.70)	0.02
Allergic rhinitis ^a	379/2,253	1	1.2 (0.85–1.6)	0.99 (0.68–1.4)	0.76 (0.49–1.2)	0.14
Hypertension ^b	638/2,232	1	1.3 (0.93–2.0)	1.5 (1.1–2.3)	2.3 (1.5–3.4)	<0.0001
Diabetes mellitus ^b	113/2,216	1	8.9 (1.7–160)	14 (2.8–260)	23 (4.6–430)	<0.0001
Hyperlipidemia ^b	976/2,229	1	1.7 (1.3–2.2)	2.4 (1.8–3.3)	3.4 (2.4–4.8)	<0.0001
Gout (men) ^b	57/1,051	1	2.9 (0.78–14)	3.4 (0.91–17)	6.2 (1.7–31)	0.007
Thyroid diseases ^a	73/2,253	1	1.0 (0.46–2.4)	1.2 (0.51–2.7)	0.74 (0.29–1.9)	0.32
Kidney disease ^a	47/2,253	1	0.53 (0.18–1.5)	0.73 (0.27–2.0)	0.49 (0.16–1.5)	0.28
Gastric ulcer ^a	196/2,253	1	1.6 (0.95–2.7)	1.0 (0.60–1.9)	0.98 (0.55–1.8)	0.29
Gynecological disease ^a	161/1,192	1	2.4 (1.3–4.5)	2.2 (1.1–4.3)	3.5 (1.7–7.2)	0.003

Profile likelihood confidence interval for adjusted odds ratios

^a Adjusted for age, sex, smoking habit, drinking habit, regional block, and survey year^b Adjusted for age, sex, smoking habit, drinking habit, regional block, survey year, and BMI^c PCDDs/PCDFs (pg/g lipid): Q1:0–6.075, Q2:6.075–9.7950, Q3:9.7950–15.05, Q4:15.05–^d DL-PCBs (pg/g lipid): Q1:0–3.2, Q2:3.2–5.6, Q3:5.6–10, Q4:10–^e Total dioxins (pg/g lipid): Q1:0–9.7, Q2:9.7–16, Q3:16–25, Q4:25–

as IL-4 and IL-5 was significantly decreased in culture supernatants of spleen cells, while concentrations of Th1-type cytokines such as interferon-gamma were increased by TCDD, without the induction of atopic dermatitis-like

lesions (Fujimaki et al. 2002). On the contrary, Tauchi et al. (2005) showed that atopic dermatitis-like skin lesions developed in transgenic mice constitutionally expressing AhR in keratinocytes, in the absence of ligands.

Table 5 Association between dioxins in blood and self-reported history of atopic dermatitis

Cases/no. of subjects		Dioxins ^g				<i>P</i> for trend
		Q1 (<25th) Reference	Q2 (25th to <50th) OR (95 % CI)	Q3 (50th to <75th) OR (95 % CI)	Q4 (≥ 75th) OR (95 % CI)	
Model 2 ^a						
PCDDs/PCDFs	116/2,225	1	0.83 (0.51–1.4)	0.63 (0.33–1.2)	0.48 (0.19–1.1)	0.06
DL-PCBs	116/2,225	1	1.2 (0.73–1.9)	1.0 (0.53–1.9)	0.45 (0.15–1.2)	0.14
Total dioxins	116/2,225	1	0.88 (0.54–1.4)	0.98 (0.53–1.8)	0.28 (0.09–0.76)	0.04
Model 3 ^b						
PCDDs/PCDFs	117/2,251	1	0.88 (0.54–1.4)	0.65 (0.34–1.2)	0.50 (0.20–1.2)	0.08
DL-PCBs	117/2,251	1	1.4 (0.85–2.3)	1.2 (0.60–2.3)	0.53 (0.16–1.5)	0.27
Total dioxins	117/2,251	1	0.89 (0.55–1.4)	1.0 (0.54–1.9)	0.29 (0.09–0.81)	0.05
Model 4 ^c						
PCDDs/PCDFs	117/2,251	1	0.86 (0.52–1.4)	0.62 (0.32–1.2)	0.46 (0.19–1.1)	0.05
DL-PCBs	117/2,251	1	1.2 (0.77–2.0)	1.0 (0.55–1.9)	0.44 (0.15–1.2)	0.12
Total dioxins	117/2,251	1	0.85 (0.52–1.4)	0.93 (0.50–1.7)	0.26 (0.08–0.71)	0.02
Model 5 ^d						
PCDDs/PCDFs	117/2,251	1	0.89 (0.54–1.4)	0.64 (0.33–1.2)	0.45 (0.18–1.0)	0.04
DL-PCBs	117/2,251	1	1.2 (0.76–2.0)	1.0 (0.54–1.9)	0.40 (0.13–1.1)	0.09
Total dioxins	117/2,251	1	0.87 (0.53–1.4)	0.92 (0.49–1.7)	0.25 (0.08–0.69)	0.02
Model 6 ^e						
PCDDs/PCDFs	116/2,239	1	0.86 (0.52–1.4)	0.63 (0.32–1.2)	0.46 (0.18–1.0)	0.04
DL-PCBs	116/2,239	1	1.2 (0.77–2.0)	1.0 (0.53–1.9)	0.44 (0.14–1.2)	0.12
Total dioxins	116/2,239	1	0.86 (0.53–1.4)	0.93 (0.50–1.7)	0.26 (0.08–0.70)	0.02
Model 7 ^f						
PCDDs/PCDFs	117/2,244	1	0.88 (0.54–1.4)	0.63 (0.33–1.2)	0.46 (0.19–1.1)	0.05
DL-PCBs	117/2,244	1	1.3 (0.77–2.0)	1.0 (0.53–1.9)	0.43 (0.14–1.1)	0.11
Total dioxins	117/2,244	1	0.87 (0.54–1.4)	0.93 (0.50–1.7)	0.26 (0.08–0.70)	0.02

Profile likelihood confidence interval for adjusted odds ratios

^a Model 2 is adjusted for age, sex, smoking habit, drinking habit, regional block, survey year, and fish

^b Model 3 is adjusted for age, sex, smoking habit, drinking habit, regional block, survey year, and DHA

^c Model 4 is adjusted for age, sex, smoking habit, drinking habit, regional block, survey year, and GLA

^d Model 5 is adjusted for age, sex, smoking habit, drinking habit, regional block, survey year, and AA

^e Model 6 is adjusted for age, sex, smoking habit, drinking habit, regional block, survey year, and meat

^f Model 7 is adjusted for age, sex, smoking habit, drinking habit, regional block, survey year, and dairy products

^g Method of classification was same as that in Table 4

Ito et al. (2008) also reported that TCDD exposure exacerbated atopic dermatitis-related inflammation with no increase in IgE antibody production in picryl chloride-sensitized NC/Nga mice. Thus, several experimental studies have showed that TCDD may decrease allergic diseases by suppressing Th2 immune responses, while other studies reported an exacerbation of atopic dermatitis-like skin disease through the involvement of other mechanisms.

Regarding hypertension, diabetes mellitus, and hyperlipidemia, the ORs significantly increased with increasing TEQ of PCDDs/PCDFs, DL-PCBs, and total dioxins in blood. The results of our study are consistent with those of previous studies in various countries. In cross-sectional

studies, background environmental exposure to 1,2,3,4,6,7,8-HeptaCDD and PCB126 was associated with an increased risk of diabetes among the US population in the 1999–2002 National Health and Nutrition Examination Survey (Lee et al. 2006; Everett et al. 2007). Serum levels of four DL-PCBs were also associated with the prevalence of metabolic syndrome in the National Health and Nutrition Examination Survey (Lee et al. 2007). In our previous study, high blood pressure, hypertriglyceridemia, and hyperglycemia were closely associated with levels of PCDDs, PCDFs, and DL-PCBs in blood (Uemura et al. 2009).

In the present study, the OR of gout significantly increased with increasing TEQ of PCDDs/PCDFs, DL-PCBs, and total

TEQ in blood. Obesity, alcohol drinking, and high intake of purine-rich foods, such as meat and fish, are known to be risk factors for the development of gout (Choi et al. 2004). On the other hand, the intake of fish, shellfish, and meat is a major route of exposure to dioxins in Japan (Tsutsumi et al. 2001; Sasamoto et al. 2006). Therefore, one explanation for this result is that common risk factors are shared by dioxin exposure and gout. Another explanation may be that exposure to dioxins is in itself a risk factor for developing gout. To our knowledge, there have been no previous epidemiologic studies that showed an association between exposure to dioxins and gout.

In this study, the OR of gynecologic diseases increased significantly with an increase in the TEQ of PCDDs/PCDFs, DL-PCBs, and total dioxins in blood. In Taiwanese Yucheng women exposed to high levels of PCDFs and DL-PCBs, frequencies of abnormal menstrual bleeding and stillbirth were high (Yu et al. 2000). In a historical cohort study performed in Seveso, Italy, the relative risk of endometriosis was 2.1 for women with increased serum 2,3,7,8-TCDD levels, but not significantly higher (Eskenazi et al. 2002). In general populations, the results of previous studies on endometriosis are inconsistent (Tsukino et al. 2005; Porpora et al. 2009). In the present study, recall bias seems unlikely because study participants had no knowledge of their blood dioxin levels at the time of the surveys. However, the category of gynecologic disease used in the questionnaire was too wide to draw an inference. Therefore, it is necessary to use a narrower definition of diseases with similar etiology in future epidemiologic studies.

The strength of the present study is the large sample size ($N = 2,264$). Additionally, the OR of atopic dermatitis for the highest quartile of total TEQ remained significantly lower than unity, even after adjustments for various confounding factors, such as frequency of consumption of fish, meat, and dairy products, or serum levels of DHA, AA, and GLA. On the other hand, our study also has some limitations. First, because of the cross-sectional approach, the temporal relationship between dioxin exposure and development of diseases remains obscure. Second, although it is known that atopic dermatitis develops mostly in infancy, blood dioxin levels were measured during adulthood. This time lag may have resulted in random measurement error in exposure variables; however, the effect may be toward an attenuation of the association. Third, information on the history of most diseases was based on self-reporting, and latent and undiagnosed patients may have been missed. In the case of misclassifications of self-reported information, the effect may also be to mask the true effects. Fourth, since the questionnaire did not ask about family history of diseases, it was not possible to take account of the effects of genetic predisposition in statistical analysis. Fifth, because of the study design, subjects living fishing villages

were oversampled compared with the general Japanese population. Thus, median blood level of dioxins in this study may have been slightly higher than that of the general population. On the other hand, oversampling of fishing villages may have resulted in the wider variation in the exposure variables (blood levels of dioxins). Even after adjustment for residential area, the OR of atopic dermatitis in the highest quartile of total TEQ was significantly lower than 1, precluding the possibility of confounding by residential area.

In conclusion, we found an inverse association between the levels of PCDDs/PCDFs and total dioxins in blood and self-reported history of atopic dermatitis in the Japanese population. Large-scale prospective studies on the association between exposure to dioxins early in life and the subsequent development of allergic diseases will be needed in the future. Background exposure to dioxins was also positively associated with hypertension, diabetes, and hyperlipidemia.

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Conflict of interest The authors declare that they have no conflict of interest.

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