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Prevalence of Metabolic Syndrome Associates with Body Burden Levels of Dioxin and Related Compounds among General Inhabitants in Japan

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Title: Prevalence of Metabolic Syndrome Associates with Body Burden Levels of Dioxin and Related Compounds among General Inhabitants in Japan

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4) Abbreviations:

Abbreviations	Definitions
Ah	aryl hydrocarbon
ATP-Ⅲ	Adult Treatment Panel Ⅲ
d.f.	degrees of freedom
DL-PCBs	dioxin-like polychlorinated biphenyls
GC/MS	gas chromatography/mass spectrometry
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein

HpCDD	heptachlorodibenzo-p-dioxin
HpCDF	heptachlorodibenzofurans
HxCDD	hexachlorodibenzo-p-dioxin
HxCDF	hexachlorodibenzofurans
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
OCDD	octachlorodibenzo-p-dioxin
OCDF	octachlorodibenzofurans
ORs	odds ratios
PCBs	polychlorinated biphenyls
PCDDs	polychlorinated dibenzo-*p*-dioxins
PCDFs	polychlorinated dibenzo-furans
PeCDD	pentachlorodibenzo-p-dioxin
PeCDF	pentachlorodibenzofurans
POPs	persistent organic pollutants
TCDD	tetrachlorodibenzo-*p*-dioxin
TCDF	tetrachlorodibenzofurans
TEF	toxic equivalency factor
TEQs	toxic equivalents

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- Abstract
- Introduction
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  - Assessment of metabolic syndrome
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Abstract

Background: It was recently reported that environmental exposure to some persistent organic pollutants associates with metabolic syndrome in the US population.

Objectives: We evaluated the associations of body burden levels of dioxins and related compounds with the prevalence of metabolic syndrome among general inhabitants in Japan.

Methods: We conducted a cross-sectional study on 1,374 participants, not occupationally exposed to these pollutants, living widely in Japan through 2002 - 2006. Lipid-adjusted concentrations of ten polychlorinated dibenzo-*p*-dioxins (PCDDs), seven polychlorinated dibenzo-furans (PCDFs), twelve dioxin-like polychlorinated biphenyls (DL-PCBs), which has a toxic equivalency factor, and biochemical factors were determined in fasting blood. A questionnaire survey was also performed.

Results: The toxic equivalents (TEQs) of PCDDs, PCDFs, DL-PCBs and total TEQ had significant adjusted associations with metabolic syndrome excluding the diabetic subjects or not. By analyzing separately for each component of metabolic syndrome, the TEQ of DL-PCBs as well as total TEQ associated with all components, and the odds ratios (ORs) in the highest quartile of the TEQ of DL-PCBs in four of the five components were higher than those of PCDDs or PCDFs. We further found congener specific associations with metabolic syndrome, particularly, the highest quartiles of PCB126 and PCB105 had adjusted ORs of 9.1 and 7.3, respectively.

Conclusions: These results suggested that body burden levels of dioxins and related compounds, particularly those of DL-PCBs, associate with metabolic syndrome. Of the components, high blood pressure, elevated triglyceride and glucose intolerance might closely associate with these pollutants.

Introduction

Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), collectively called dioxins, are produced through the burning of garbage and some types of chemical manufacturing processes. Legal regulations of dioxins in the 1990s in Japan have achieved a 95% reduction in their emissions from incinerators (Ministry of the Environment, Japan 2004). Some forms of polychlorinated biphenyls (PCBs), which are included in another group of persistent organic pollutants (POPs), exhibit toxic actions similar to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), then are called dioxin-like PCBs (DL-PCBs). PCDDs/PCDFs and DL-PCBs are widely persistent in the environment because they are lipophilic and resistant to biological and chemical degradation. Several congeners of these pollutants exhibit various biological and toxic actions, such as dermal toxicity, immunotoxicity, carcinogenicity and adverse effects on reproductive, neurobehavioral and endocrine functions (Lindström et al. 1995; Weisglas-Kuperus 1998). Recently, these actions are suggested to be induced by low-level exposure to these pollutants (Johnson et al. 2001; Lee et al. 2006).

Metabolic syndrome, characterized by a cluster of metabolic disorders including central obesity, glucose intolerance, dyslipidemia and hypertension, has been increasing in the developed countries (Flegal et al. 2002; Ford 2005). The impact of each component may be small, however, the impact of the co-occurrence of plural components may be considerably greater than any one alone (Nakanishi et al. 2003). Subjects suffering from metabolic syndrome are suggested to be at increased risk of type 2 diabetes (Lorenzo et al. 2003; Sattar et al. 2003) and cardiovascular diseases (Lakka et al. 2002; Malik et al. 2004; McNeill et al. 2005). Recently, background environmental exposure to some POPs has been reported to associate with increased risk of diabetes (Lee et al. 2006), and additionally with increased risk of metabolic syndrome (Lee et al. 2007), in the US population in the 1999-2002 National

Health and Nutrition Examination Survey (NHANES). Metabolic syndrome has become widely prevalent in the population in Asian countries including Japan, however, it is not evaluated whether similar associations exist among the Asian population. A survey on the accumulation of dioxins and related compounds in humans has been carried out from 2002 under the supervision of the Ministry of the Environment**,** Government of Japan. In this paper, we report the recent 5-year results of a cross-sectional study to evaluate the associations of body burden levels of PCDDs, PCDFs and DL-PCBs with the prevalence of metabolic syndrome, and with the prevalence of its components, among general inhabitants in Japan.

Materials and Methods

Survey areas and participants

This survey was conducted from 2002 to 2006 in Japan on 1,374 participants (627 male and 747 female) aged 15-73 years. The selection of survey areas and the recruitment of the participants were previously reported (Uemura et al. 2008). Briefly, the whole of Japan was divided into five regional blocks shown in Table 1, and single prefecture was selected from each regional block every survey year. Approximately 50 individuals were recruited in each prefecture, almost 20 were from urban areas, almost 15 were from farming village areas and almost 15 were from fishing village areas, with almost equally in age and gender among the three areas. As a whole, the subjects participated from 75 different residential areas of 25 prefectures through 5 survey years, and evenly distributed in age and gender among the urban, farming and fishing village areas in each survey year. Participants were required to have been living in residing area for at least 10 years, to have had no known occupational exposure to PCDDs/PCDFs and DL-PCBs and to have no known severe anemia or other health problems

that interfere with blood sampling. Participation in this study was essentially voluntary, and after the details of this survey was explained, written informed consent was obtained from each participant. We designed to recruit at least 250 participants every survey year, and excluded subjects due to known severe anemia or other health problems were few during the survey years. The study protocol was reviewed and approved by the Ethical Committee of the Ministry of the Environment, Government of Japan.

Questionnaire

The participants were requested to complete a questionnaire to obtain data on individual characteristics including body height and weight, residential and occupational histories, smoking and drinking habits, past history of diseases and treatments. Regarding drinking habits, subjects were asked how often they had consumed beer, sake, shochu (rough distilled spirits) and whisky over the previous month. The frequency of each item in the questionnaire was classified into five degrees; almost everyday, 3-4 times/week, 1-2 times/week, 1-2 times/month, and almost never. These five degrees were expressed as times/week; 6, 3.5, 1.5, 0.35 and 0.1, respectively. We did not specify the unit or portion of each item. The frequency of alcohol consumption was summarized as the sum of the frequency of each item, then divided into three categories; regular; >= 6 times/week, often; 1.5 to < 6 times/week, rarely or never; < 1.5 times/week.

Measurements

Approximately 25 ml of fasting venous blood was obtained from each participant, and 20 ml was collected into vacutainer tubes containing sodium-heparin solutions (VT-100H, Terumo, Tokyo, Japan or 367677, Becton, Dickson and Company, Tokyo, Japan). Analyses of PCDDs, PCDFs and DL-PCBs in whole blood were performed at the Institute of General

Science for the Environment, METOCEAN Environment (currently IDEA Consultants, Inc.), Shizuoka, Japan, by isotope dilution high-resolution gas chromatography/mass spectrometry (GC/MS), after liquid/liquid extraction and gel clean-up. The detailed analytical procedure of these chemicals has been previously reported (Nakamura et al. 2008). Blood lipid (%) was measured gravimetrically using sulfuric ammonium-ethanol/hexane technique. Seven congeners of PCDDs, ten congeners of PCDFs and twelve congeners of DL-PCBs, which has a toxic equivalency factor (TEF), were determined. The limit of detection was 1 pg/g lipid for PCDDs/PCDFs with 4–5 chlorine atoms, 2 pg/g lipid for PCDDs/PCDFs with 6–7 chlorine atoms, 4 pg/g lipid for PCDDs/PCDFs with 8 chlorine atoms, and 10 pg/g lipid for DL-PCBs.

Toxic equivalent (TEQ) was calculated using the 1998 WHO TEF (Van den Berg et al. 1998). If the level of the pollutant was below the limit of detection, zero was used as its concentration.

Biochemical factors including high-density lipoprotein (HDL)-cholesterol, triglyceride and hemoglobin A1c (HbA1c) in the blood were determined with an automatic biochemical analyzer (Hitachi 7450, Japan).

Blood pressure was measured in each subject at resting sitting. If a measurement was extremely high or low or far from everyday value, it was tried again after a short rest and the second measurement was used as the final measurement.

Assessment of metabolic syndrome

The prevalence of metabolic syndrome was assessed by using the modification of the National Cholesterol Education Program (NCEP) Adult Treatment Panel Ⅲ (ATP-Ⅲ) definition (NCEP ATP-Ⅲ 2002). Some studies in Asia have suggested that the criteria of central obesity proposed by the NCEP ATP-Ⅲ, which was based on the data from Caucasians, was inappropriate for Asian populations whose build were generally smaller than Caucasians

(Ko et al. 2005; Tan et al. 2004). Therefore, we diagnosed a subject as metabolic syndrome when satisfying three or more of the following five criteria: 1) a body mass index ≥ 25 kg/m^2 instead of an abdominal waist circumference; 2) serum triglyceride ≥150 mg/dl; 3) serum HDL-C < 40 mg/dl in men or < 50 mg/dl in women; 4) a systolic blood pressure ≥ 130 mmHg and/or a diastolic blood pressure ≥ 85 mmHg, or self-report answer of a history of physician-diagnosed hypertension; 5) a HbA1c ≥ 5.6 % instead of fasting serum glucose, or self-reported answer of a history of physician-diagnosed diabetes.

The associations of diabetes mellitus with PCBs and other POPs are well-established, and diabetes mellitus is a partial component of metabolic syndrome. Therefore, we further investigated the associations of these pollutants with metabolic syndrome by excluding diabetes mellitus from the definition of metabolic syndrome. When prevalent diabetes was excluded from the analyses, the subjects satisfying the following criteria were excluded : (1) self-report answer of a history of physician-diagnosed diabetes, or (2) plasma HbA1c > 6.1%. It was reported that HbA1c > 6.1% predicts fasting plasma glucose ≥ 126mg/dl, the standard for determining diabetes, with a sensitivity of 63.2% and a specificity of 97.4% (Rohlfing et al. 2000).

Statistical analysis

The sex difference of body mass indexes was evaluated by the Wilcoxon rank-sum test. We analyzed the associations of the TEQs of PCDDs, PCDFs, DL-PCBs and total TEQ with the prevalence of metabolic syndrome by excluding prevalent diabetes or not in logistic regressions, non-adjusted and adjusted for age, sex, smoking and drinking habits, regional block, residential area and survey year. We also tested the adjusted associations of the TEQs with the five components of metabolic syndrome in logistic regressions. We further evaluated separately the adjusted associations of the concentrations of the selected 16 congeners, for

which more than 75% of the subjects had concentrations higher than the limit of detection, with the prevalence of metabolic syndrome in logistic regressions. Analyzed isomers were 1,2,3,7,8-pentachlorodibenzo-p-dioxin (PeCDD), 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin (HxCDD), 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin (HpCDD), octachlorodibenzo-p-dioxin (OCDD), 2,3,4,7,8-pentachlorodibenzofurans (PeCDF), 1,2,3,6,7,8-hexachlorodibenzofurans (HxCDF), PCB126, PCB169, PCB105, PCB114, PCB118 , PCB123, PCB156, PCB157, PCB167 and PCB189. In these analyses, the first quartile (< 25 percentile) was defined as the reference, and dummy variables for sex, regional block, residential area, survey year, smoking habit and drinking habit were created and those except for reference categories were included in the model. Tests of trend were conducted using the median value for each quartile of the TEQs or the concentrations of the congeners in logistic models. All statistical analyses were performed with the SAS software package (version 8.2, SAS Institute Inc., Cary, NC). All P values are two-tailed and those less than 0.05 were considered statistically significant.

Results

The baseline characteristics of the participants are shown in Table 1. Of the 1,374 subjects, 627 (45.6 %) were male and 747 (54.4 %) were female. The median (25th-75th percentile) of body mass index were 23.4 (21.6-25.7) kg/m^2 and 21.6 (20.0-23.9) kg/m^2 in male and female subjects, respectively, with a significant difference ($P < 0.001$). Table 2 shows the prevalence of metabolic syndrome and its five components in the subjects. Of the 1,374 subjects, 160 (11.6 %) subjects were defined as metabolic syndrome, including 105 men and 55 women. High blood pressure had a higher prevalence rate than the other components.

Table 3 lists the values of the concentration and TEQ for each congener of PCDDs, PCDFs and DL-PCBs in the blood of the subjects. The medians of the TEQs of PCDDs, PCDFs, DL-PCBs and total TEQ were 7.4 pg TEQ/g lipid, 4.5 pg TEQ/g lipid, 7.6 pg TEQ/g lipid and 20 pg TEQ/g lipid, respectively.

Table 4 indicates the non-adjusted and adjusted associations of the TEQs with the prevalence of metabolic syndrome. All of the TEQs of PCDDs, PCDFs, DL-PCBs and total TEQ had significant non-adjusted and adjusted associations with the prevalence of metabolic syndrome (tests of trend were all significant). The highest quartile of total TEQ had a high adjusted OR (95%CI) of 5.3 (2.3 - 13) compared to the reference. Table 5 indicates the non-adjusted and adjusted associations of the TEQs with the prevalence of metabolic syndrome excluding the subjects with prevalent diabetes. Sixty five subjects were diagnosed as prevalent diabetes, and 38 subjects were with metabolic syndrome among the 65 diabetic subjects. Finally, 122 subjects were defined as metabolic syndrome when prevalent diabetes was excluded from the analyses. When prevalent diabetes was excluded, the adjusted associations of the TEQs of DL-PCBs with metabolic syndrome were strengthened, while those of PCDFs were slightly attenuated (p for trend was 0.07).

The adjusted associations of the TEQs with the prevalence of each component of metabolic syndrome are shown in Table 6. All of the TEQs of PCDDs, PCDFs, DL-PCBs and total TEQ associated with high blood pressure and elevated triglyceride (tests of trend were all significant). The TEQs of PCDDs, DL-PCBs and total TEQ showed trends for the associations with high HbA1c (p for trends were all < 0.01). In particular, the highest quartiles of DL-PCBs and total TEQ had adjusted ORs of 8.0 and 8.6, respectively in the prevalence of high HbA1c. Of note, the TEQ of DL-PCBs as well as total TEQ showed trends for the associations with all five components of metabolic syndrome, and the ORs in the highest quartile of the TEQ of DL-PCBs in four of the five components were higher than those of

PCDDs or PCDFs. In contrast, the TEQ of PCDFs did not have associations with high body mass index (p for trend = 0.56) or low HDL-cholesterol (p for trend = 0.12).

Table 7 indicates the adjusted associations of the concentrations of the selected congeners with the prevalence of metabolic syndrome. Significant trends for the associations with metabolic syndrome were found for 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, OCDD, 2,3,4,7,8-PeCDF, PCB126, PCB105, PCB114, PCB118 , PCB123 and PCB167. Especially, the highest quartiles of PCB126 and PCB105 had considerable high adjusted ORs (95%CI) of 9.1 (4.1 - 21) and 7.3 (3.4 - 17), respectively, compared to the respective references.

Discussion

Several studies on veterans exposed to high levels of dioxins have suggested that one of the plausible diseases associated with dioxins is type 2 diabetes (Henriksen et al.1997; Michalek et al. 1999). This association is supported by similar epidemiologic studies, whose subjects were exposed to high levels of dioxins in Seveso, Italy (Pesatori et al. 2003) and were Korean Vietnam veterans exposed to Agent Orange (Kim et al. 2003). However, a causal association of dioxins or other POPs with diabetes is far from established. Recently, it has been reported that low levels exposure to dioxins associate with increased risk of diabetes (Lee et al. 2006), and additionally with increased risk of metabolic syndrome (Lee et al. 2007), in the US population in the 1999-2002 National Health and Nutrition Examination Survey (NHANES). Metabolic syndrome, whose pathogenesis is based on the central obesity, has been increasing in Asian countries including Japan due to the westernization of life-style. We studied whether similar associations found in US population exist among Japanese population. Lee et al. investigated the associations between some POPs and metabolic syndrome among

non-diabetic subjects. However, if diabetic subjects were excluded, the selected subjects might be less representative among general inhabitants. Therefore, we did not exclude the diabetic subjects in basal analyses, and additionally examined the associations by excluding diabetic subjects.

We found that all of the TEQs of PCDDs, PCDFs, DL-PCBs and total TEQ had significant non-adjusted and adjusted associations with the prevalence of metabolic syndrome. The highest quartile of total TEQ had a high adjusted OR of 5.3. By analyzing for each component of metabolic syndrome, all of the TEQs of PCDDs, PCDFs, DL-PCBs and total TEQ associated with high blood pressure and elevated triglyceride. The TEQs of PCDDs, DL-PCBs and total TEQ showed significant trends for the associations with high HbA1c. In particular, the highest quartiles of DL-PCBs and total TEQ had high adjusted ORs of 8.0 and 8.6, respectively in the prevalence of high HbA1c. In another point of view, the TEQ of DL-PCBs as well as total TEQ associated with all five components of metabolic syndrome, and the ORs in the highest quartile of the TEQ of DL-PCBs in four of the five components were higher than those of PCDDs or PCDFs. From these findings, of the five components of metabolic syndrome, high blood pressure, elevated triglyceride and glucose intolerance may closely associate with these pollutants, particularly with DL-PCBs. In contrast, high body mass index did not have associations with the TEQs except of DL-PCBs. Of the five components, high body mass index might have less close association with the exposure to these pollutants. TEQ based analyses can be justified if the mechanism is through aryl hydrocarbon (Ah) receptor. PCDDs/PCDFs and DL-PCBs assigned a toxicity equivalent factor are known to exhibit various biological and toxic actions through binding with Ah receptors, therefore we conducted the TEQ based analyses. However, Lee et al. recently reported that the background exposure to some POPs may be closely related to metabolic syndrome, with different POPs related to different metabolic syndrome traits (Lee et al. 2007).

We wondered if Ah receptor-mediated mechanism of the examined pollutants may not be critical in their link to metabolic syndrome, therefore we further analyzed the associations of the concentration of each congener separately with the prevalence of metabolic syndrome. Then, we found that 12 of the selected sixteen congeners, which were widely distributed to any of PCDDs, PCDFs and DL-PCBs, had trends for the associations with metabolic syndrome. In particular, the highest quartiles of PCB126 and PCB105 had considerable high adjusted odds ratios of 9.1 and 7.3, respectively, and this finding was consistent with that of the TEQ based analyses.

We found the associations of the TEQs of PCDDs and PCDFs with the prevalence of metabolic syndrome, however Lee et al. found no such associations (Lee et al. 2007). These associations in our TEQ based analyses agreed with the results of our congener specific analyses. Lee et al. also reported that the risk of metabolic syndrome reached to the highest in the third quartile and then plateaued in the case of DL-PCBs (Lee et al. 2007), while we found a significant trend for the association between the TEQ of DL-PCBs and metabolic syndrome. This association in our study persisted or rather strengthened when diabetic subjects were excluded from the analyses. Although we could not clearly explain this discrepancy between the findings of Lee et al and ours, the difference in prevalence of metabolic syndrome (24.3% and 9.3%, respectively, when excluding diabetic subjects) might influence this discrepancy (Lee et al. 2007).

The associations observed in this cross-sectional study should be carefully interpreted in cause-effect relations. As for diabetic subjects, a slower elimination of dioxins was not supported by a study on Vietnam veterans, which reported no difference in TCDD half-life between diabetic and non-diabetic subjects (Michalek et al. 2003). However, as for the subjects with metabolic syndrome, whether an elimination of dioxins is slower or not has not been investigated. Some previous studies have shown that individuals with higher BMI,

which was one component of metabolic syndrome in our study, have reduced dioxin clearance (Blanck et al. 2000; Flesch-Janys et al. 1996). Therefore, suffering from metabolic syndrome might impair the metabolism or the excretion of these pollutants and might lead to a greater accumulation in the body. Further prospective studies will be needed to clarify this causality.

Metabolic syndrome has recently become prevalent, while the body burden levels of PCDDs/PCDFs and DL-PCBs have a decreasing trend (Konishi et al. 2001; Porta 2006; Wittsiepe et al. 2000). Therefore, the dose-response relations of the TEQs or the concentrations of these pollutants in the blood with metabolic syndrome observed in this study or another (Lee et al. 2007) seem conflicting. One possible explanation is that toxic actions of these pollutants may be strengthened in obesity. This explanation is supported by recent molecular epidemiological study for diabetogenic effects of dioxin exposure. This study has reported an inverse correlation between the ratio of GLUT4 to nuclear factor kappa B and serum dioxin concentrations in obesity and family history of diabetes (Fujiyoshi et al. 2006). To clarify this hypothesis in our data, we further analyzed the associations between the concentrations of these pollutants and the prevalence of each component of metabolic syndrome except BMI after stratifying by BMI ($\geq$ 25 kg/m^2 and $<$ 25 kg/m^2). However, the associations did not show expected tendencies (data not shown), therefore the reliability of this hypothesis should be further verified. Another explanation is that PCDDs/PCDFs or DL-PCBs contribute to the occurrence of metabolic syndrome, however, other factors including the westernization of life-style also affect the occurrence of metabolic syndrome.

The strength of the present study is that our subjects were recent representatives of the general inhabitants in Japan. This study has several limitations. First, as stated above, the findings in this study should be interpreted with caution in cause-effect relationships because of the cross-sectional design. Second, we diagnosed metabolic syndrome using a criteria of a body mass index instead of a waist circumference, however a body mass index could not

rigorously reflect the central obesity. Similarly, we used HbA1c as one of the criteria instead of fasting serum glucose, because we did not have data on fasting serum glucose.

In conclusion, this recent representative data among general inhabitants in Japan showed significant associations of body burden levels of dioxins and related compounds with the prevalence of metabolic syndrome. Of the five components, high blood pressure, elevated triglyceride and glucose intolerance may closely associate with the blood levels of these pollutants, especially with DL-PCBs. Basic studies in animals and further epidemiological studies using longitudinal designs should be further conducted to define the mechanism and the causality between exposure to these pollutants and metabolic syndrome.

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Table 1 Baseline characteristics of the participants (n = 1,374)

	Both sexes (n=1,374) (%)	Male (n=627) (%)	Female (n=747) (%)
Age (years)			
15-29	20.7	22.7	19.0
30-39	18.7	20.6	17.1
40-49	21.9	20.3	23.3
50-59	24.0	23.3	24.6
60-73	14.7	13.2	15.9
Regional block			
Hokkaido/Tohoku	19.9	19.1	20.5
Kanto/Koshin'etsu	20.0	17.2	22.4
Tokai/Hokuriku/Kinki	20.5	24.4	17.3
Chugoku/Shikoku	19.3	21.2	17.7
Kyushu/Okinawa	20.3	18.0	22.2
Residential area			
Urban	40.2	37.6	42.3
Farming village	32.0	33.0	31.2
Fishing village	27.8	29.4	26.5
Survey year			
2002	18.9	18.7	19.0
2003	19.8	19.6	20.0
2004	19.2	17.9	20.4
2005	21.0	21.5	20.5
2006	21.2	22.3	20.2
Smoking habit			
Current	21.8	40.2	6.3
Past	13.1	22.0	5.6
Never	64.6	37.5	87.4
Unknown	0.5	0.3	0.7
Drinking habit			
Regular	20.7	36.8	7.1
Often	22.3	27.3	18.2
Rarely or never	53.7	32.7	71.4
Unknown	3.3	3.2	3.3

Table 2 Prevalence of metabolic syndrome and its five components in the participants

	Both sexes (n=1,374) (%)	Male (n=627) (%)	Female (n=747) (%)
Metabolic syndrome			
yes	11.6	16.7	7.4
no	87.0	81.5	91.6
unknown	1.4	1.8	1.1
Components			
Body mass index ≥ 25 kg/m^2			
yes	23.7	32.4	16.5
no	75.3	66.2	82.9
unknown	1.0	1.4	0.7
Blood pressure ≥ 130/85 mmHg or a history of physician-diagnosed hypertension			
yes	41.3	50.4	33.7
no	58.6	49.6	66.1
unknown	0.1	0.0	0.1
Triglyceride ≥ 150 mg/dl			
yes	16.2	26.3	7.8
no	83.5	73.4	92.0
unknown	0.3	0.3	0.3
HDL-cholesterol < 40 mg/dl in men or 50 mg/dl in women			
yes	10.3	10.4	10.3
no	89.4	89.3	89.4
unknown	0.3	0.3	0.3
HbA1c ≥ 5.6 % or a history of physician-diagnosed diabetes			
yes	11.2	13.4	9.4
no	88.8	86.6	90.6
unknown	0.0	0.0	0.0

Metabolic syndrome was diagnosed when satisfying three or more of the five components

Table 3 The concentration and TEQ for each congener of PCDDs, PCDFs and DL-PCBs in the blood of the subjects

Congener	Concentration (pg/g lipid) Median (25% - 75%)	TEF	TEQ (pg TEQ/g lipid) Median (25% - 75%)
2,3,7,8-TCDD	1.0 (0.0 - 2.0)	1	1.0 (0.0 - 2.0)
1,2,3,7,8-PeCDD	5.0 (3.0 - 7.0)	1	5.0 (3.0 - 7.0)
1,2,3,4,7,8-HxCDD	0.0 (0.0 - 3.0)	0.1	0.0 (0.0 - 0.30)
1,2,3,6,7,8-HxCDD	15 (9.0 - 21)	0.1	1.5 (0.90 - 2.1)
1,2,3,7,8,9-HxCDD	3.0 (0.0 - 4.0)	0.1	0.30 (0.0 - 0.40)
1,2,3,4,6,7,8-HpCDD	12 (9.0 - 18)	0.01	0.12 (0.09 - 0.18)
OCDD	140 (89 - 230)	0.0001	0.01 (0.01 - 0.02)
total PCDDs			7.4 (4.6 - 11.2)
2,3,7,8-TCDF	1.0 (0.0 - 2.0)	0.1	0.10 (0.0 - 0.20)
1,2,3,7,8-PeCDF	0.0 (0.0 - 0.0)	0.05	0.0 (0.0 - 0.0)
2,3,4,7,8-PeCDF	7.0 (5.0 - 11.0)	0.5	3.5 (2.5 - 5.5)
1,2,3,4,7,8-HxCDF	3.0 (0.0 - 4.0)	0.1	0.30 (0.0 - 0.40)
1,2,3,6,7,8-HxCDF	3.0 (2.0 - 5.0)	0.1	0.30 (0.20 - 0.50)
1,2,3,7,8,9HxCDF	0.0 (0.0 - 0.0)	0.1	0.0 (0.0 - 0.0)
2,3,4,6,7,8-HxCDF	0.0 (0.0 - 2.0)	0.1	0.0 (0.0 - 0.20)
1,2,3,4,6,7,8-HpCDF	2.0 (0.0 - 3.0)	0.01	0.02 (0.0 - 0.03)
1,2,3,4,7,8,9-HpCDF	0.0 (0.0 - 0.0)	0.01	0.0 (0.0 - 0.0)
OCDF	0.0 (0.0 - 0.0)	0.0001	0.0 (0.0 - 0.0)
total PCDFs			4.5 (2.9 - 6.8)
total PCDDs/PCDFs			12 (7.7 -18)
PCB 77	0.0 (0.0 - 0.0)	0.0001	0.0 (0.0 - 0.0)
PCB 81	0.0 (0.0 - 0.0)	0.0001	0.0 (0.0 - 0.0)
PCB 126	40 (22 - 78)	0.1	4.0 (2.2 - 7.8)
PCB 169	30 (20 - 50)	0.01	0.30 (0.20 - 0.50)
non-ortho PCBs			4.4 (2.4 - 8.3)
PCB 105	1300 (750 - 2400)	0.0001	0.13 (0.08 - 0.24)
PCB 114	460 (250 - 830)	0.0005	0.23 (0.13 - 0.42)
PCB 118	7500 (4200 - 13000)	0.0001	0.75 (0.42 - 1.3)
PCB 123	100 (60 - 200)	0.0001	0.01 (0.01 - 0.02)
PCB 156	2800 (1500 - 4800)	0.0005	1.4 (0.75 - 2.4)
PCB 157	770 (420 - 1300)	0.0005	0.39 (0.21 - 0.65)
PCB 167	1300 (730 - 2300)	0.00001	0.01 (0.01 - 0.02)
PCB 189	320 (180 - 580)	0.0001	0.03 (0.02 - 0.06)
mono-orthoPCBs			3.0 (1.6 - 5.1)
total DL-PCBs			7.6 (4.4 - 13)
total TEQ			20 (12 - 31)

TEF; toxic equivalency factor, TEQs; toxicity equivalents, TCDD; tetrachlorodibenzo-*p*-dioxin, PeCDD; pentachlorodibenzo-*p*-dioxin, HxCDD; hexachlorodibenzo-*p*-dioxin, HpCDD; heptachlorodibenzo-*p*-dioxin, OCDD; octachlorodibenzo-*p*-dioxin, PCDDs; polychlorinated dibenzo-*p*-dioxins, TCDF; tetrachlorodibenzofurans, PeCDF; pentachlorodibenzofurans, HxCDF; hexachlorodibenzofurans, HpCDF; heptachlorodibenzofurans, OCDF; octachlorodibenzofurans, PCDFs; polychlorinated dibenzofurans, PCBs; polychlorinated biphenyls

Table 4 Non-adjusted and adjusted associations of the TEQs of PCDDs, PCDFs, DL-PCBs and total TEQ with the prevalence of metabolic syndrome

	No. of subjects	No. of cases	Non-adjusted odds ratio (95%CI)	Adjusted odds ratio [a] (95%CI)
PCDDs				
< 4.60	343	15	Referent	Referent
≥ 4.60 and < 7.39	344	39	2.8 (1.5 - 5.4)	2.2 (1.2 - 4.4)
≥ 7.39 and < 11.20	339	38	2.7 (1.5 - 5.2)	2.1 (1.1 - 4.3)
≥ 11.20	348	68	5.4 (3.1 - 10)	3.2 (1.6 - 6.7)
p for trend			<0.01	<0.01
PCDFs				
< 2.90	330	9	Referent	Referent
≥ 2.90 and < 4.50	347	40	4.6 (2.3 - 10)	4.0 (1.9 - 9.3)
≥ 4.50 and < 6.80	352	48	5.6 (2.9 - 12)	4.1 (1.9 - 9.7)
≥ 6.80	345	63	8.0 (4.1 - 17)	4.4 (2.0 - 11)
p for trend			<0.01	0.04
DL-PCBs				
< 4.40	339	14	Referent	Referent
≥ 4.40 and < 7.60	339	27	2.0 (1.1 - 4.1)	1.9 (0.95 - 4.0)
≥ 7.60 and < 13.00	325	39	3.2 (1.7 - 6.2)	2.8 (1.3 - 6.2)
≥ 13.00	371	80	6.4 (3.6 - 12)	4.8 (2.2 - 11)
p for trend			<0.01	<0.01
Total TEQ				
< 12.00	303	10	Referent	Referent
≥ 12.00 and < 20.00	363	29	2.6 (1.3 - 5.6)	2.3 (1.1 - 5.3)
≥ 20.00 and < 31.00	353	47	4.5 (2.3 - 9.7)	3.7 (1.7 - 8.7)
≥ 31.00	355	74	7.7 (4.1 - 16)	5.3 (2.3 - 13)
p for trend			<0.01	<0.01

PCDDs; polychlorinated dibenzo-*p*-dioxins, PCDFs; polychlorinated dibenzofurans, PCBs; polychlorinated biphenyls, TEQs; toxicity equivalents

[a] Adjusted for age, gender, smoking habit, drinking habit, regional block, residential area and survey year (model d.f. = 19)

Metabolic syndrome was diagnosed when satisfying three or more of the following five criteria: 1) a body mass index ≥ 25 kg/m^2; 2) serum triglyceride ≥150 mg/dl; 3) serum HDL-C < 40 mg/dl in men or < 50 mg/dl in women; 4) a systolic blood pressure ≥ 130 mmHg and/or a diastolic blood pressure ≥ 85 mmHg, or a history of physician-diagnosed hypertension; 5) a HbA1c ≥ 5.6 % or a history of physician-diagnosed diabetes.

Table 5 Non-adjusted and adjusted associations of the TEQs of PCDDs, PCDFs, DL-PCBs and total TEQ with the prevalence of metabolic syndrome excluding the subjects with prevalent diabetes.

	No. of subjects	No. of cases	Non-adjusted odds ratio (95%CI)	Adjusted odds ratio [a] (95%CI)
PCDDs				
< 4.49	325	12	Referent	Referent
≥ 4.49 and < 7.27	329	31	2.7 (1.4 - 5.6)	2.2 (1.1 - 4.8)
≥ 7.27 and < 11.00	311	28	2.6 (1.3 - 5.3)	2.1 (0.99 - 4.7)
≥ 11.00	344	51	4.6 (2.5 - 9.2)	3.4 (1.6 - 7.6)
p for trend			<0.01	<0.01
PCDFs				
< 2.83	326	9	Referent	Referent
≥ 2.83 and < 4.40	326	31	3.7 (1.8 - 8.3)	3.5 (1.6 - 8.2)
≥ 4.40 and < 6.60	323	37	4.5 (2.2 - 10)	3.8 (1.7 - 9.2)
≥ 6.60	334	45	5.5 (2.8 - 12)	3.8 (1.6 - 9.7)
p for trend			<0.01	0.07
DL-PCBs				
< 4.28	327	9	Referent	Referent
≥ 4.28 and < 7.40	320	24	2.9 (1.4 - 6.7)	3.1 (1.4 - 7.4)
≥ 7.40 and < 12.87	334	35	4.2 (2.1 - 9.4)	5.0 (2.1 - 13)
≥ 12.87	328	54	6.9 (3.5 - 15)	7.3 (2.9 - 20)
p for trend			<0.01	<0.01
Total TEQ				
< 12.00	303	10	Referent	Referent
≥ 12.00 and < 19.00	318	22	2.2 (1.0 - 4.9)	2.2 (0.98 - 5.0)
≥ 19.00 and < 30.00	345	35	3.3 (1.7 - 7.2)	3.2 (1.4 - 7.6)
≥ 30.00	343	55	5.6 (2.9 - 12)	5.1 (2.1 - 13)
p for trend			<0.01	<0.01

PCDDs; polychlorinated dibenzo-*p*-dioxins, PCDFs; polychlorinated dibenzofurans, PCBs; polychlorinated biphenyls, TEQs; toxicity equivalents

[a] Adjusted for age, gender, smoking habit, drinking habit, regional block, residential area and survey year (model d.f. = 19)

Table 6 Adjusted ORs and 95% CIs of the prevalence of each component of metabolic syndrome by quartiles of the TEQs of PCDDs, PCDFs, DL-PCBs and total TEQ

	Q1	Q2	Q3	Q4	p for trend
1) Body mass index ≥ 25 kg/m^2					
PCDDs	Referent	1.5 (0.97 - 2.2)	1.5 (0.93 - 2.3)	1.5 (0.91 - 2.4)	0.30
PCDFs	Referent	1.3 (0.85 - 2.0)	1.5 (0.97 - 2.4)	1.3 (0.79 - 2.2)	0.56
DL-PCBs	Referent	1.7 (1.1 - 2.6)	1.8 (1.1 - 3.0)	2.6 (1.5 - 4.7)	<0.01
Total TEQ	Referent	1.3 (0.86 - 2.1)	1.9 (1.2 - 3.1)	1.9 (1.1 - 3.3)	0.07
2) Blood pressure ≥ 130/85 mmHg or a history of physician-diagnosed hypertension					
PCDDs	Referent	0.99 (0.68 - 1.4)	1.0 (0.70 - 1.6)	1.6 (1.0 - 2.5)	0.01
PCDFs	Referent	1.3 (0.92 - 2.0)	1.6 (1.1 - 2.4)	1.9 (1.2 - 3.0)	<0.01
DL-PCBs	Referent	1.0 (0.71 - 1.6)	1.1 (0.69 - 1.7)	1.9 (1.1 - 3.1)	<0.01
Total TEQ	Referent	1.3 (0.86 - 1.9)	1.2 (0.81 - 1.9)	1.9 (1.1 - 3.1)	<0.01
3) Triglyceride ≥ 150 mg/dl					
PCDDs	Referent	2.1 (1.3 - 3.5)	2.1 (1.2 - 3.7)	2.7 (1.5 - 4.8)	<0.01
PCDFs	Referent	1.5 (0.87 - 2.5)	2.1 (1.2 - 3.6)	2.2 (1.2 - 4.1)	0.02
DL-PCBs	Referent	2.4 (1.4 - 4.3)	3.4 (1.8 - 6.6)	5.2 (2.6 - 11)	<0.01
Total TEQ	Referent	2.0 (1.1 - 3.5)	3.0 (1.6 - 5.6)	3.8 (1.9 - 7.5)	<0.01
4) HDL-cholesterol < 40 mg/dl in men or 50 mg/dl in women					
PCDDs	Referent	1.5 (0.83 - 2.8)	1.8 (0.93 - 3.4)	3.2 (1.7 - 6.4)	<0.01
PCDFs	Referent	1.5 (0.85 - 2.8)	2.0 (1.0 - 3.7)	1.9 (0.98 - 4.0)	0.12
DL-PCBs	Referent	1.1 (0.58 - 1.9)	1.9 (0.98 - 3.8)	2.1 (0.98 - 4.5)	0.06
Total TEQ	Referent	1.3 (0.72 - 2.5)	1.9 (0.97 - 3.8)	2.7 (1.3 - 5.9)	<0.01
5) HbA1c ≥ 5.6 % or a history of physician-diagnosed diabetes					
PCDDs	Referent	2.7 (1.2 - 6.6)	3.5 (1.6 - 8.7)	4.6 (2.0 - 12)	<0.01
PCDFs	Referent	2.1 (0.93 - 5.2)	3.9 (1.8 - 9.6)	3.2 (1.4 - 8.3)	0.06
DL-PCBs	Referent	2.1 (0.90 - 5.3)	3.1 (1.3 - 8.0)	8.0 (3.2 - 22)	<0.01
Total TEQ	Referent	3.3 (1.3 - 10)	4.5 (1.7 - 14)	8.6 (3.1 - 28)	<0.01

Q1; 1st quartile, Q2; 2nd quartile, Q3; 3rd quartile, Q4; 4th quartile
Adjusted for age, gender, smoking habit, drinking habit, regional block, residential area and survey year (model d.f. = 19)

Table 7 Adjusted ORs and 95% CIs of the prevalence of metabolic syndrome by quartiles of the concentrations of the selected congeners

	Q1	Q2	Q3	Q4	p for trend
1,2,3,7,8-PeCDD	Referent	2.8 (1.2 - 8.4)	2.0 (0.77 - 6.4)	3.7 (1.4 - 12)	0.04
1,2,3,6,7,8-HxCDD	Referent	2.5 (1.3 - 5.6)	3.0 (1.4 - 6.7)	3.6 (1.7 - 8.2)	<0.01
1,2,3,4,6,7,8-HpCDD	Referent	2.1 (1.1 - 3.8)	3.0 (1.7 - 5.5)	4.5 (2.4 - 8.6)	<0.01
OCDD	Referent	1.9 (1.1 - 3.5)	3.0 (1.7 - 5.5)	3.7 (2.0 - 6.9)	<0.01
2,3,4,7,8-PeCDF	Referent	3.8 (1.7 - 9.8)	4.1 (1.8 - 11)	5.3 (2.2 - 14)	<0.01
1,2,3,6,7,8-HxCDF	Referent	1.2 (0.40 - 3.7)	2.9 (1.3 - 7.9)	2.8 (1.2 - 8.0)	0.06
PCB 126	Referent	2.5 (1.1 - 5.6)	4.9 (2.4 - 11)	9.1 (4.1 - 21)	<0.01
PCB 169	Referent	1.7 (0.78 - 4.2)	1.7 (0.79 - 4.2)	1.4 (0.60 - 3.7)	0.73
PCB 105	Referent	1.9 (0.87 - 4.2)	4.6 (2.3 - 9.9)	7.3 (3.4 - 17)	<0.01
PCB 114	Referent	3.1 (1.5 - 7.1)	3.6 (1.6 - 8.7)	6.4 (2.7 - 17)	<0.01
PCB 118	Referent	2.5 (1.3 - 5.3)	3.8 (1.8 - 8.3)	6.5 (3.0 - 15)	<0.01
PCB 123	Referent	1.8 (0.90 - 3.7)	3.4 (1.7 - 6.9)	5.9 (2.8 - 13)	<0.01
PCB 156	Referent	1.5 (0.76 - 3.2)	1.7 (0.78 - 3.7)	2.0 (0.84 - 4.9)	0.23
PCB 157	Referent	1.3 (0.65 - 2.5)	1.1 (0.51 - 2.3)	1.2 (0.54 - 2.8)	0.81
PCB 167	Referent	2.3 (1.1 - 4.8)	2.7 (1.3 - 6.1)	4.1 (1.8 - 9.7)	<0.01
PCB 189	Referent	0.69 (0.34 - 1.4)	1.1 (0.54 - 2.3)	0.98 (0.42 - 2.3)	0.79

PeCDD; pentachlorodibenzo-*p*-dioxin, HxCDD; hexachlorodibenzo-*p*-dioxin, HpCDD; heptachlorodibenzo-*p*-dioxin,
OCDD; octachlorodibenzo-*p*-dioxin, PeCDF; pentachlorodibenzofurans, HxCDF; hexachlorodibenzofurans,
PCBs; polychlorinated biphenyls
Adjusted for age, gender, smoking habit, drinking habit, regional block, residential area and survey year (model d.f. = 19)
Metabolic syndrome was diagnosed when satisfying three or more of the following five criteria:
1) a body mass index $\geq$ 25 kg/m^2; 2) serum triglyceride $\geq$150 mg/dl; 3) serum HDL-C < 40 mg/dl in men or < 50 mg/dl in women;
4) a systolic blood pressure $\geq$ 130 mmHg and/or a diastolic blood pressure $\geq$ 85 mmHg, or a history of physician-diagnosed hypertension;
5) a HbA1c $\geq$ 5.6 % or a history of physician-diagnosed diabetes.