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Association of Brominated Flame Retardants with Diabetes and Metabolic syndrome in the United States Population: 2003-2004

Ji-Sun Lim, M.D., Ph.D.,[1] Duk-Hee Lee, M.D., Ph.D.,[1] David R. Jacobs, Jr., Ph.D.[2, 3]

[1]Department of Preventive Medicine and Health Promotion Research Center, School of Medicine, Kyungpook National University, Daegu, Korea
[2]Department of Epidemiology, School of Public Health, University of Minnesota, Minnesota, USA
[3]Department of Nutrition, University of Oslo, Oslo, Norway

Corresponding Author:
Duk-Hee Lee
E-mail: lee_dh@knu.ac.kr

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Objective: Chlorinated Persistent Organic Pollutants (POPs), endocrine disruptors accumulated in adipose tissue, were associated with diabetes and metabolic syndrome. Brominated flame retardants (BFR) such as polybrominated diphenyl ethers (PBDEs) or polybrominated biphenyls (PBBs) are another class of POPs for which body burden is increasing. Cross-sectional associations of serum concentrations of BFRs with diabetes and metabolic syndrome were studied.

Research Design and Methods: In the National Health and Nutrition Examination Survey 2003-2004, 1,367 adult were examined with respect to diabetes status. Five PBDEs and one PBB were selected, detectable in ≥60% of participants. For the outcome metabolic syndrome, we restricted the analysis to 637 participants with a morning fasting sample.

Results: Compared to subjects with serum concentrations below the limit of detection, prevalent diabetes had differing dose-response associations with serum concentrations of PBB-153 and PBDE-153. Adjusted odds ratios across quartiles of serum concentrations for PBB-153 or PBDE-153 were 1.0, 0.7, 1.4, 1.6, and 1.9 (P for trend<0.01) and 1.0, 1.6, 2.6, 2.7, and 1.8 (P for quadratic term<0.01), respectively. PBB-153 was also positively associated with the prevalence of metabolic syndrome with adjusted odds ratios of 1.0, 1.5, 3.1, 3.1, and 3.1 (P for trend<0.01). As in its association with diabetes, PBDE-153 showed an inverted U-shaped association with metabolic syndrome.

Conclusions: Pending confirmation in prospective studies, lipophilic xenobiotics including brominated POPs stored in adipose tissue may be involved in the pathogenesis of diabetes and metabolic syndrome.

We have recently reported strong cross-sectional associations of serum concentrations of chlorinated Persistent Organic Pollutants (POPs) with diabetes (1,2). In addition to diabetes, POPs were associated with most components of metabolic syndrome, although specific associations differed depending on chemicals (3). Based on both these epidemiological and previous experimental findings, we have proposed that POPs stored in adipose tissue may play a key role in the pathogenesis of metabolic syndrome and type 2 diabetes (4). As well-known endocrine disruptors, their persistence in adipose tissue may disturb normal function of lipid and glucose metabolism in adipose tissue (4).

These lipophilic pollutants are a mixture of several hundred chemicals with similar properties such as resistance to biodegradation and bioaccumulation in adipose tissue. Aside from the chlorinated POPs we studied before (dioxins, furans, polychlorinated biphenyls (PCBs), or organochlorine (OC) pesticides), there are other important subclasses of POPs. Among them, chemicals belonging to brominated flame retardants (BFRs) are of special interest because of the recent marked increase in levels of polybrominated diphenyl ethers (PBDEs), the most well-known class of BFR, in humans as well as in the environment (5,6). PBDEs are extensively used in a variety of consumer products such as home/office furnishings and electronics as flame retardants, and their body burdens in North America are much higher than those of Europeans (5).

Similar to chlorinated POPs, BFRs bioaccumulate in adipose tissue in living organisms and are suspected to be endocrine disruptors (7). Such lipophilic xenobiotics in adipose tissue have been suspected to disrupt hormonal signaling in adipose tissue as endocrine disruptors (8, 9). They are chemically and toxicologically similar to PCBs, which were strongly associated with hyperglycemia and dyslipidemia in our previous studies (5). Thus, BFRs may also be associated with disturbance of lipid and glucose metabolism.

Serum concentrations of biologically important BFRs were measured in subsamples of the National Health and Examination Survey (the NHANES) 2003-2004 (10). Our analyses were performed to investigate associations of prevalence of diabetes and metabolic syndrome with the serum concentrations of BFRs.

METHODS

The NHANES, conducted annually since 1999 by the Centers for Disease Control and Prevention (CDC), is an ongoing survey designed to measure the health and nutritional status of the civilian noninstitutionalized U.S. population (11). The surveys include household interviews, standardized physical examinations, and collection of medical histories and biologic specimens. Some of these specimens were used to assess exposure to environmental chemicals (10). Among 9,643 participants in The NHANES 2003-2004, PBDEs and PBBs were measured in serum from a random one-third subsample of subjects aged 12 years and older.

The NHANES standardized home interview was followed by a detailed physical examination in a mobile evaluation clinic or the participant's home. Venous blood samples were collected and shipped weekly at -20°C. Waist circumference was measured at the high point of the iliac crest to the nearest 0.1 cm at the end of normal expiration. Serum triglyceride concentration was measured enzymatically and high-density lipoprotein (HDL) cholesterol concentration was analyzed using the direct HDL cholesterol immunoassay method. Up to four blood pressure measurements were obtained from each participant. To establish high blood

pressure status, we used the average of the last two measurements of blood pressure for participants who had three or four measurements, the last measurement for participants with only two measurements, and the only measurement for participants who had one measurement. Plasma glucose was measured with a hexokinase enzymatic reference method. BFRs were measured by high-resolution gas chromatography/high-resolution mass spectrometry using isotope dilution for quantification. The BFRs were reported on a lipid adjusted basis using concentrations of serum total cholesterol and triglycerides. Among 11 BFRs measured in the NHANES, we selected the 5 PBDEs (PBDE-28, PBDE-47, PBDE-99, PBDE-100, and PBDE-153) and 1 polybrominated biphenyl (PBB, PBB-153 selected) for which at least 60% of study subjects had concentrations more than the limit of detection (LOD). A total of 1,367 study participants aged 20 years and older with information on serum concentrations of 6 BFRs and fasting or random plasma glucose were included for analysis.

Participants were considered to have diabetes mellitus if 1) their fasting plasma glucose was ≥126 mg/dL, 2) their non-fasting plasma glucose was ≥200 mg/dL, or 3) they were taking insulin or an oral agent. Exclusion of non-fasting subjects did not greatly change the estimates.

We defined the metabolic syndrome among fasting participants using the National Cholesterol Education Program definition. This definition required that the participant satisfied three or more of the following five criteria: waist circumference ≥102 cm in men and ≥ 88 cm in women; 2) fasting triglycerides ≥ 150 mg/dL; 3) HDL-cholesterol <40 mg/dL in men and < 50 mg/dL in women; 4) blood pressure ≥ 130/85 mmHg or on anti-hypertensive medication; 5) fasting-glucose ≥ 100 mg/dL or on anti-diabetic medication. Among the 1,367 study subjects, 655 participants had information on fasting morning samples suitable for measurement of triglycerides and glucose. After excluding 18 subjects with missing data on waist circumference, the final sample size was 637.

For each BFR, participants with serum concentrations under levels of LOD were regarded as the reference group and those with detectable values categorized by cutpoints at the 25th, 50th, and 75th percentiles. Logistic regression models were used to calculate multivariable-adjusted odd ratios (OR). Variables considered to be confounders in the multivariable analysis were age, gender, race/ethnicity, poverty income ratio (the ratio of income to the family's poverty threshold; higher poverty income ratio means wealthier), and body mass index. In the case of metabolic syndrome, we further considered cigarette smoking (never, former, or current), cotinine concentrations (ng/mL), alcohol consumption (g/day) and leisure time physical activity (vigorous, moderate, or none) as possible confounders. In 149 participants, we substituted median values of the remaining participants for missing poverty income ratio, body mass index, cotinine concentrations, or alcohol consumption; exclusion of these individuals did not materially alter any estimates. When associations did not look linear, we also fit quadratic models.

All statistical analyses were performed with SAS 9.1 and SUDAAN 9.0. Estimates of main results were calculated accounting for stratification and clustering, adjusting for age, race and ethnicity, and poverty income ratio instead of using sample weights; this adjustment has been regarded as a good compromise between efficiency and bias (12). As results were very similar with SAS 9.1 and SUDAAN 9.0, we present the results based on SAS 9.1.

RESULTS

The sample of 1367 participants included 47.3% men and 53.3% white race. Mean ± standard deviation for age and BMI were 49.7 ± 19.3 years and 28.3 ± 5.9 kg/m^2. In general, PBB-153 showed different patterns of associations with demographic factors from PBDEs, except PBDE-153 (Table 1). Among 6 BFRs, only PBB-153 was positively associated with age while PBDEs showed no or inverse associations with age. In addition, participants with high PBB-153 tended to be men and white race, and to have high socioeconomic status. However, most PBDEs were not associated with gender, tended to be higher among non-white race, and to be found in participants with low socioeconomic status. Both PBB-153 and PBDE-153 were inversely associated with BMI while other PBDEs were not associated with BMI. Serum concentrations of PBB-153 were not associated with those of PBDEs, except for a weak correlation with PBDE-153. All 5 PBDEs were strongly and positively associated among each other.

There were 156 diabetic cases among 1367 participants (prevalence 11.4%). The associations with diabetes depended on BFR (Table 2). After adjusting for age, sex, race, poverty income ratio, and BMI, there was a significant positive association across 5 categories of PBB-153 with diabetes prevalence, with adjusted odds ratios of 1.0, 0.7, 1.4, 1.6, and 1.9 (P for trend<0.01). Among 5 PBDEs, there was a non-linear association with diabetes across 5 categories of serum concentrations of PBDE-153; adjusted odds ratios were 1.0, 1.6, 2.6, 2.7, and 1.8 (P for quadratic term<0.01). Although both PBDE-99 and PBDE-100 tended to show inverted U-shaped associations similar with PBDE-153, they failed to reach statistical significance. Neither PBDE-28 nor PBDE-47 was associated with diabetes. Further adjustment for waist circumference did not change these results (data not shown).

Metabolic syndrome had a prevalence of 37.2% (237/637). There was a positive association with the prevalence of metabolic syndrome across 5 categories of serum PBB-153 concentration, with adjusted odds ratios of 1.0, 1.5, 3.1, 3.1, and 3.1 (P for trend<0.01) (Table 3). Similar to the association with diabetes, PBDE-153 showed an inverted U-shaped association with metabolic syndrome with adjusted odds ratios of 1.0, 2.1, 2.5, 2.4, and 1.7 (P for quadratic term=0.02).

When we separately studied the 5 components of metabolic syndrome, PBB-153 was non-linearly associated with waist circumference, high triglyceride, and low HDL-cholesterol (P for quadratic terms =0.09, <0.01, and 0.07, respectively). PBB-153 tended to be positively associated with high fasting glucose, but did not reach statistical significance. However, PBB-153 was significantly associated with glycemia, defined using the higher cutoff-point for fasting glucose of ≥ 110 mg/dL instead of ≥ 100 mg/dL (data not shown). PBDE-153 also showed an inverted U-shaped association with high triglycerides (P for quadratic term<0.01). Waist circumference or fasting glucose also showed some non-linear trends, but none were significant.

DISCUSSION

In this paper we continued our examination of the relationships of POPs with diabetes and metabolic syndrome by studying BFRs. Among 6 BFRs, PBB-153 and PBDE-153 were significantly associated with both diabetes and metabolic syndrome although dose-response relationships did not appear to be the same between these two chemicals. Thus, these data provide limited support for the proposition that, besides chlorinated POPs, other chemicals with properties of persistence in adipose tissue and endocrine disruptors may also disturb glucose and lipid metabolism.

However, evidence in favor of this conclusion is much stronger for chlorinated

POPs (1-3) than for the brominated POPs which were the focus of this paper. In our previous studies on chlorinated POPs (1-3), most chemicals belonging to the PCB and OC pesticide classes showed strong associations with diabetes and metabolic syndrome. Despite the chemical and physical similarities among PCBs, PBBs, or PBDEs, most chemicals belonging to PBDEs, except PBDE-153, were not clearly associated with diabetes and metabolic syndrome.

In fact, there is an important difference in exposure route of PBDEs from chlorinated POPs or PBBs. At first, like chlorinated POPs, the diet was regarded as a major pathway of exposure to PBDEs, because they also bioaccumulate in food chains (13). However, recent studies discovered that the main exposure route of PBDEs in the general population is house dust, not diet, because they are used as additives to retard fire and flames in a variety of commercial and household products (14). Human are exposed to PBDEs in house dust in direct inhalation, ingestion, and dermal exposure (5). Unlike PBDEs, PBBs were prohibited in the USA in the 1970s after an accidental human exposure in Michigan (15). Thus, their main exposure route would be diet similar to chlorinated POPs (15). These different exposure routes were reflected in the correlations among serum BFR concentrations. Serum concentrations of 5 chemicals belonging to PBDEs showed very strong mutual correlations, consistent with common exposure sources. However, serum PBB-153 concentration showed at most weakly positive associations in comparison to associations with PBDEs. As PBDEs were measured among the NHANES participants in whom PCBs were not measured, we could not examine the correlation between PCBs and PBDEs. However, other studies with simultaneously measurement reported no association between these two chemicals (16).

Therefore, serum concentrations of chlorinated POPs or PBBs with exposure primarily through food may reflect a cumulative lifetime dose of exposure. However, serum concentrations of PBDEs may be a mixture of more recent exposure to indoor pollution and cumulative low exposure to diet. These considerations appeared to be well reflected in the associations with age. PBBs and chlorinated POPs (1-3) were strongly associated with age while most PBDEs were not or even inversely associated with age. Unlike traditional toxicological effects due to acute high dose exposure, disturbance of glucose and lipid metabolism due to POPs in adipose tissue as endocrine disruptors may require long-term exposure. Thus, we think that serum concentrations of PBDEs may not reflect a biologically important long-term dose. Furthermore, toxicological studies have shown that different exposure routes led to different pharmacokinetics in terms of uptake, distribution, and elimination (17).

However, PBDE-153 tended to stand out from other PBDEs in several ways. Even though PBDE-153 showed an inverse association with age, opposite to that of PBB-153, serum concentrations of PBDE-153, compared with other PBDEs, were more positively correlated with those of PBB-153. In addition, both the higher concentrations in men and the inverse association with BMI were similar to those of PBB-153, but different from other PBDEs. It may be that PBDE-153 has different pharmacokinetics from other PBDEs.

The significant associations of PBB-153 and PBDE-153 need further discussion in relation to their differing dose-response curves. Interestingly, in our previous studies, we also found non -linear dose-response relations of PCBs with various outcomes, including plateaus or inverted U-shaped associations (1-3). Among various subclasses of POPs, PCBs are the subclass which has most similar structures to BFRs (5). Thus,

similar dose-response curve between PCBs and BFRs may be biologically plausible. In fact, in addition to PCBs, most chlorinated POPs showed an association that was much steeper across lower background concentrations than across higher background concentrations. Although a linear dose-response relation is generally regarded by epidemiologists as a criterion for causality, the possibility of inverted U-shaped associations with endocrine disruptors has been suggested by some experimental studies; a strong effect across low doses, but a weakened or no effect at high dose (18). Although researchers cautioned that low dose effects cannot be extrapolated from animal studies to human (19), our findings on PCB, PBBs, or PBDEs suggest that this concept might also apply in the human body.

This non-linear dose-response curve may explain previous epidemiological findings in the Michigan cohort with accidental high exposure to PBBs (20). In fact, this prospective cohort study did not show any association between PBB concentrations and incident diabetes. However, serum concentrations of the reference group in Michigan cohort were already much higher than those of current participants. No association in subjects with high exposure to POPs but strong associations in subjects with background exposure to POPs were similarly observed with chlorinated POPs (21).

Even though it is still unclear what biological mechanism is involved in the association of POPs with diabetes and metabolic syndrome, the potential of xenobiotics to disrupt glucose and lipid metabolism in mammals is a well-developed theory in toxicology (8). Indeed, many of the early toxicity responses in animal studies with a range of pollutants note glucosuria, dyslipidaemia, increased gluconeogenesis, and fatty liver (8). Furthermore, dioxin-like compounds exert their effects through binding to the aryl-hydrocarbon receptor which is thought to antagonise peroxisome proliferator-activated receptors (9).

The inverse association of PBB-153 and PBDE-153 with BMI was interesting. In fact, both of these POPs showed positive associations with waist circumference after adjusting for BMI. In our previous studies (1-3), PCBs were also inversely associated with BMI, but positively associated with waist circumference while other chlorinated POPs were weakly and positively associated both BMI and waist circumference. The exposure to POPs may affect visceral adipose tissue differently than subcutaneous adipose tissue and these effects may depend on POPs subclass. Furthermore, even though POPs are generally observed to be positively associated with obesity, associations between POPs and obesity would not be simple. For example, a high intake of fatty food is related to both a high POPs exposure and obesity. On the contrary, an increase of adipose tissue mass itself dilutes the concentrations of POPs. Furthermore, some experimental studies have reported that the exposure to endocrine disruptors itself can induce obesity (22). As these mechanisms do not all act in the same direction, the associations between POPs and obesity may be diverse.

This study has several limitations. First of all, the current finding should be interpreted with caution due to the cross-sectional nature of this study. Even though our results are biologically plausible because some PBDEs are reported to cause the disturbance of glucose and lipid metabolism in adipose tissue (7), we could not exclude the possibility that changes in metabolic state due to disease could have created the associations we observed. Second, BFRs were not measured in the same population as chlorinated POPs in the NHANES, so we could not simultaneously consider the effect of chlorinated POPs. There may be a possibility of synergistic effects that multiple POPs reinforce each other's toxicity in the

general population as we discussed before (21). Third, inference should be made cautiously in light of the multiple comparisons intrinsic in this investigation.

Along with our previous findings on chlorinated POPs, our current study suggests that the background exposure to some brominated POPs may be closely related to disturbance of glucose and lipid metabolism in general population. Prospective study of the relation of POPs with diabetes and metabolic syndrome is needed because both the exposure and the disease have substantial prevalence and the public health significance of such a relation could be marked.

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Table 1. Spearman correlation coefficients* between 6 brominated flame retardants (BFRs) with age, sex, race, poverty income ratio, and body mass index (number of participants =1,367)

	2,2',4,4',5,5'-hexabromophenyl(PBB-153)	2,4,4'-tribromodiphenyl ether(PBDE-28)	2,2',4,4'-tetrabromodiphenyl ether(PBDE-47)	2,2',4,4',5-pentabromodiphenyl ether(PBDE-99)	2,2',4,4',6-pentabromodiphenyl ether(PBDE-100)	2,2',4,4',5.5'-hexabromodiphenyl ether(PBDE-153)
Age	+0.38‡	+0.04	-0.03	-0.05	-0.07†	-0.09‡
Men	+0.21‡	+0.02	+0.03	+0.03	+0.04	+0.15‡
White race	+0.13‡	-0.05	-0.06†	-0.08‡	-0.06†	+0.03
Poverty income ratio	+0.06†	-0.06†	-0.06†	-0.07‡	-0.07†	-0.06†
Body mass index	-0.14‡	+0.03	-0.002	-0.03	-0.02	-0.16‡
PBB-153	1	+0.06	+0.02	+0.01	+0.05	+0.15‡
PBDE-28		1	+0.87‡	+0.76‡	+0.81‡	+0.55‡
PBDE-47			1	+0.90‡	+0.93‡	+0.62‡
PBDE-99				1	+0.85‡	+0.57‡
PBDE-100					1	+0.76‡
PBDE-153						1

* : Detectable values of each BFRs were individually ranked to calculate correlation coefficients; all not detectable values were ranked as 0

† : P<0.05

‡ : P<0.01

Table 2. Adjusted* odds ratio (OR) and 95% confidence interval (CI) of prevalent diabetes by category of 6 brominated flame retardants (BFRs) (number of participants =1,367)

Analyte		Not detectable	Detectable					
			<25th†	25th-<50th	50th-<75th	≥75th	P_{trend}‡	$P_{quadratic}$
PBB-153	Conc. (ng/g of lipid)†	-	1.2	2.3	3.8	13.1		
	Cases/no.	11/166	16/306	39/303	41/292	49/300		
	Adjusted* OR (95% CI)	Referent	0.7 (0.3-1.6)	1.4 (0.7-3.0)	1.6 (0.8-3.5)	1.9 (0.9-4.0)	<0.01	0.88
PBDE-28	Conc. (ng/g of lipid)†	-	0.7	1.2	2.0	5.4		
	Cases/no.	37/279	19/296	32/262	31/259	37/271		
	Adjusted* OR (95% CI)	Referent	0.5 (0.3-1.0)	1.2 (0.7-2.0)	0.9 (0.5-1.6)	0.8 (0.5-1.4)	0.93	0.97
PBDE-47	Conc. (ng/g of lipid)†	-	6.5	13.7	28.2	73.3		
	Cases/no.	2/36	43/333	34/333	40/332	37/333		
	Adjusted* OR (95% CI)	Referent	3.4 (0.8-15.7)	2.9 (0.6-13.5)	3.8 (0.8-17.4)	2.7 (0.6-12.5)	1.00	0.16
PBDE-99	Conc. (ng/g of lipid)†	-	3.1	5.3	9.2	26.9		
	Cases/no.	45/456	37/231	25/222	22/230	27/228		
	Adjusted* OR (95% CI)	Referent	2.0 (1.2-3.2)	1.5 (0.9-2.6)	1.2 (0.7-2.2)	1.3 (0.7-2.2)	0.57	0.06
PBDE-100	Conc. (ng/g of lipid)†	-	1.4	2.8	5.6	16.8		
	Cases/no.	10/94	37/330	37/305	35/322	37/316		
	Adjusted* OR (95% CI)	Referent	1.3 (0.6-2.8)	1.6 (0.7-3.5)	1.6 (0.7-3.5)	1.4 (0.6-3.0)	0.50	0.20
PBDE-153	Conc. (ng/g of lipid)†	-	1.9	3.6	6.6	24.6		
	Cases/no.	9/101	34/317	40/314	42/316	31/319		
	Adjusted* OR (95% CI)	Referent	1.6 (0.7-3.6)	2.6 (1.2-5.8)	2.7 (1.2-6.0)	1.8 (0.8-4.0)	0.15	<0.01

***** Adjusted for age, sex, race, poverty income ratio, and body mass index

† : Conc, displayed is the median serum concentration in each category

‡ : P_{trend} was calculated without a quadratic term in the model, while $p_{quadratic}$ was calculated including the linear term.

Table 3. Adjusted* odds ratio (OR) and 95% confidence interval (CI) of prevalent metabolic syndrome by category of 6 brominated flame retardants (BFRs) (number of participants =637)

Analyte		Not detectable	Detectable					
			<25th†	25th-<50th	50th-<75th	≥75th	P_{trend}‡	$P_{quadratic}$
PBB-153	Conc. (ng/g of lipid)†	-	1.2	2.3	3.8	13.1		
	Cases/no.	18/82	38/137	65/145	59/137	57/136		
	Adjusted* OR (95% CI)	Referent	1.5 (0.7-3.2)	3.1 (1.4-6.5)	3.1 (1.4-6.7)	3.1 (1.4-6.9)	<0.01	0.07
PBDE-28	Conc. (ng/g of lipid)†	-	0.7	1.2	2.0	5.4		
	Cases/no.	50/142	41/149	44/107	50/116	52/123		
	Adjusted* OR (95% CI)	Referent	0.8 (0.4-1.5)	1.7 (0.9-3.1)	1.5 (0.8-2.8)	1.3 (0.7-2.4)	0.09	0.49
PBDE-47	Conc. (ng/g of lipid)†	-	6.5	13.7	28.2	73.3		
	Cases/no.	6/20	64/170	58/161	55/142	54/144		
	Adjusted* OR (95% CI)	Referent	1.1 (0.3-3.5)	0.8 (0.3-2.8)	1.2 (0.4-4.0)	1.1 (0.3-3.6)	0.70	0.72
PBDE-99	Conc. (ng/g of lipid)†	-	3.1	5.3	9.2	26.9		
	Cases/no.	82/223	50/122	34/99	37/88	34/105		
	Adjusted* OR (95% CI)	Referent	1.1 (0.7-2.0)	1.0 (0.6-1.8)	1.9 (1.0-3.5)	0.8 (0.5-1.5)	0.75	0.24
PBDE-100	Conc. (ng/g of lipid)†	-	1.4	2.8	5.6	16.8		
	Cases/no.	16/52	67/164	53/136	47/144	54/141		
	Adjusted* OR (95% CI)	Referent	1.8 (0.8-4.1)	1.5 (0.6-3.4)	1.6 (0.7-3.6)	1.7 (0.7-3.8)	0.68	0.61
PBDE-153	Conc. (ng/g of lipid)†	-	1.9	3.6	6.6	24.6		
	Cases/no.	19/52	65/162	54/133	52/143	47/147		
	Adjusted* OR (95% CI)	Referent	2.1 (1.0-4.6)	2.5 (1.1-5.6)	2.4 (1.0-5.3)	1.7 (0.7-3.8)	0.69	0.02

* Adjusted for age, sex, race, poverty income ratio, body mass index, cigarette smoking, serum cotinine, alcohol consumption and exercise

† : Conc, displayed is the median serum concentration in each category

‡ : P_{trend} was calculated without a quadratic term in the model, while $p_{quadratic}$ was calculated including the linear term.

Table 4. Adjusted* odds ratio (OR) and 95% confidence interval (CI) of prevalence of 5 components of metabolic syndrome by category of PBB-153 and PBDE-153

	Not detectable	Detectable					
		<25th†	25th-<50th	50th-<75th	≥75th	P_{trend}‡	$P_{quadratic}$
Waist circumference >102cm in men or >88cm in women							
PBB-153	Referent	1.3 (0.4-4.1)	3.5 (1.1-11.7)	2.4 (0.7-8.1)	2.1 (0.6-7.2)	0.28	0.09
PBDE-153	Referent	2.4 (0.6-9.3)	2.2 (0.6-8.6)	1.9 (0.5-7.4)	2.8 (0.7-10.8)	0.40	0.78
Triglyceride ≥ 1.7 mmol/l							
PBB-153	Referent	3.2 (1.6-6.5)	4.2 (2.1-8.7)	3.7 (1.7-7.8)	3.8 (1.8-8.0)	<0.01	<0.01
PBDE-153	Referent	4.3 (1.9-9.5)	3.5 (1.5-7.9)	3.7 (1.6-8.4)	3.2 (1.4-7.5)	0.35	<0.01
HDL-cholesterol < 1.1 mmol/l in men or < 1.4 mmol/l in women							
PBB-153	Referent	2.1 (1.1-4.2)	2.4 (1.2-4.9)	2.5 (1.2-5.2)	2.5 (1.2-5.2)	0.05	0.07
PBDE-153	Referent	0.9 (0.4-1.9)	1.6 (0.8-3.4)	1.1 (0.5-2.3)	1.1 (0.5-2.3)	0.79	0.29
Blood pressure ≥ 130/85 mmHg							
PBB-153	Referent	0.7 (0.3-1.4)	1.3 (0.6-2.5)	0.8 (0.4-1.7)	0.7 (0.3-1.4)	0.47	0.33
PBDE-153	Referent	1.4 (0.7-2.9)	1.6 (0.7-2.4)	1.5 (0.7-3.3)	1.3 (0.6-2.9)	0.65	0.23
Fasting glucose ≥ 5.6 mmol/l							
PBB-153	Referent	1.0 (0.5-2.0)	1.2 (0.6-2.4)	1.2 (0.6-2.4)	1.6 (0.8-3.2)	0.11	0.63
PBDE-153	Referent	1.8 (0.9-3.8)	1.4 (0.6-2.9)	1.5 (0.7-3.1)	1.2 (0.6-2.5)	0.51	0.24

*:Adjusted for age, sex, race, poverty income ratio, body mass index, cigarette smoking, serum cotinine, alcohol consumption and exercise

‡: P_{trend} was calculated without a quadratic term in the model, while $p_{quadratic}$ was calculated including the linear term.