

# Association of Brominated Flame Retardants With Diabetes and Metabolic Syndrome in the U.S. Population, 2003–2004

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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 (BFRs), 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 adults were examined with respect to diabetes status. Five PBDEs and one PBB were selected, detectable in  $\geq 60\%$  of participants. For the outcome metabolic syndrome, we restricted the analysis to 637 participants with a morning fasting sample.

**RESULTS** — Compared with 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.

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**W**e 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 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 (NHANES) 2003–2004 (10). Our analyses were performed to investigate associations of prevalence of diabetes and metabolic syndrome with the serum concentrations of BFRs.

## RESEARCH DESIGN AND METHODS

The NHANES, conducted annually since 1999 by the Centers for Disease Control and Prevention, 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 ex-

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Table 1—Spearman correlation coefficients between six BFRs with age, sex, race, poverty income ratio, and BMI (n = 1,367)\*

|                         | 2,2',4,4',5,5'-<br>hexabromodiphenyl<br>(PBB-153) | 2,4,4'-<br>tribromodiphenyl<br>ether (PBDE-28) | 2,2',4,4'-<br>tetrabromodiphenyl<br>ether (PBDE-47) | 2,2',4,4',5-<br>pentabromodiphenyl<br>ether (PBDE-99) | 2,2',4,4',6-<br>pentabromodiphenyl<br>ether (PBDE-100) | 2,2',4,4',5,5'-<br>hexabromodiphenyl<br>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<br>ratio | +0.06‡  | −0.06‡   | −0.06‡  | −0.07†  | −0.07‡   | −0.06‡   |
| BMI                     | −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 BFR were individually ranked to calculate correlation coefficients; all undetectable values were ranked as 0. † $P < 0.01$ . ‡ $P < 0.05$ .

posure 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  $\geq 12$  years.

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  $-20^{\circ}\text{C}$ . 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 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 five PBDEs (PBDE-28, PBDE-47, PBDE-99, PBDE-100, and PBDE-153) and one polybrominated biphenyl (PBB; PBB-153 selected) for which at least 60% of study

subjects had concentrations more than the limit of detection. A total of 1,367 study participants aged  $\geq 20$  years with information on serum concentrations of six BFRs and fasting or random plasma glucose were included for analysis. Participants were considered to have diabetes if 1) their fasting plasma glucose was  $\geq 126$  mg/dl, 2) their nonfasting plasma glucose was  $\geq 200$  mg/dl, or 3) they were taking insulin or an oral agent. Exclusion of nonfasting 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: 1) waist circumference  $\geq 102$  cm in men and  $\geq 88$  cm in women, 2) fasting triglycerides  $\geq 150$  mg/dl, 3) HDL cholesterol  $< 40$  mg/dl in men and  $< 50$  mg/dl in women, 4) blood pressure  $\geq 130/85$  mmHg or on antihypertensive medication, and 5) fasting glucose  $\geq 100$  mg/dl or on antidiabetes medication. Among 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 limit of detection were regarded as the reference group and those with detectable values categorized by cut points at the 25th, 50th, and 75th percentiles. Logistic regression models were used to calculate multivariable-adjusted odd ratios. Variables considered to be confounders in the multivariable analysis were age, sex, race/ethnicity, poverty in-

come ratio (the ratio of income to the family's poverty threshold; higher poverty income ratio means wealthier), and BMI. 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, BMI, 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 1,367 participants included 47.3% men (53.3% white). Means  $\pm$  SD for age and BMI were  $49.7 \pm 19.3$  years and  $28.3 \pm 5.9$  kg/m<sup>2</sup>, respectively. In general, PBB-153 showed different patterns of association with demographic factors from PBDEs, except PBDE-153 (Table 1). Among six BFRs, only PBB-153 was positively associated with age, while PBDEs showed no or inverse associations with age. In addition,

Table 2—Adjusted odds ratio (OR) and 95% CI of prevalent diabetes by category of six BFRs (n = 1,367)\*

| Analyte                                    | Not detectable | Detectable     |                |                |                | P trend‡ | P quadratic |
|--|----------------|----------------|----------------|----------------|----------------|----------|-------------|
|  |                | <25th†         | 25th to <50th  | 50th to <75th  | ≥75th          |          |             |
| <b>PBB-153</b>                             |                |                |                |                |                |          |             |
| Median serum concentration (ng/g of lipid) | —              | 1.2            | 2.3            | 3.8            | 13.1           |          |             |
| Cases/n                                    | 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        |
| <b>PBDE-28</b>                             |                |                |                |                |                |          |             |
| Median serum concentration (ng/g of lipid) | —              | 0.7            | 1.2            | 2.0            | 5.4            |          |             |
| Cases/n                                    | 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        |
| <b>PBDE-47</b>                             |                |                |                |                |                |          |             |
| Median serum concentration (ng/g of lipid) | —              | 6.5            | 13.7           | 28.2           | 73.3           |          |             |
| Cases/n                                    | 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        |
| <b>PBDE-99</b>                             |                |                |                |                |                |          |             |
| Median serum concentration (ng/g of lipid) | —              | 3.1            | 5.3            | 9.2            | 26.9           |          |             |
| Cases/n                                    | 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        |
| <b>PBDE-100</b>                            |                |                |                |                |                |          |             |
| Median serum concentration (ng/g of lipid) | —              | 1.4            | 2.8            | 5.6            | 16.8           |          |             |
| Cases/n                                    | 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        |
| <b>PBDE-153</b>                            |                |                |                |                |                |          |             |
| Median serum concentration (ng/g of lipid) | —              | 1.9            | 3.6            | 6.6            | 24.6           |          |             |
| Cases/n                                    | 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 BMI. †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.

participants with high PBB-153 tended to be white men and to have high socioeconomic status. However, most PBDEs were not associated with sex, tended to be higher among nonwhites, and tended 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 five PBDEs were strongly and positively associated among each other.

There were 156 diabetic case subjects among 1,367 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 five 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 five PBDEs, there was a nonlinear association with diabetes across five categories of serum concentrations of PBDE-153, with adjusted odds ratios of 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 of 637). There was a positive association with the prevalence of metabolic syndrome across five 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 associ-

ation 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 five components of metabolic syndrome, PBB-153 was nonlinearly associated with waist circumference, high triglycerides, 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

Table 3—Adjusted odds ratio (OR) and 95% CI of prevalent metabolic syndrome by category of six BFRs (n = 637)\*

| Analyte                                    | Not detectable | Detectable    |               |               |               | P trend‡ | P quadratic |
|--|----------------|---------------|---------------|---------------|---------------|----------|-------------|
|  |                | <25th†        | 25th to <50th | 50th to <75th | ≥75th         |          |             |
| <b>PBB-153</b>                             |                |               |               |               |               |          |             |
| Median serum concentration (ng/g of lipid) | —              | 1.2           | 2.3           | 3.8           | 13.1          |          |             |
| Cases/n                                    | 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        |
| <b>PBDE-28</b>                             |                |               |               |               |               |          |             |
| Median serum concentration (ng/g of lipid) | —              | 0.7           | 1.2           | 2.0           | 5.4           |          |             |
| Cases/n                                    | 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        |
| <b>PBDE-47</b>                             |                |               |               |               |               |          |             |
| Median serum concentration (ng/g of lipid) | —              | 6.5           | 13.7          | 28.2          | 73.3          |          |             |
| Cases/n                                    | 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        |
| <b>PBDE-99</b>                             |                |               |               |               |               |          |             |
| Median serum concentration (ng/g of lipid) | —              | 3.1           | 5.3           | 9.2           | 26.9          |          |             |
| Cases/n                                    | 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        |
| <b>PBDE-100</b>                            |                |               |               |               |               |          |             |
| Median serum concentration (ng/g of lipid) | —              | 1.4           | 2.8           | 5.6           | 16.8          |          |             |
| Cases/n                                    | 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        |
| <b>PBDE-153</b>                            |                |               |               |               |               |          |             |
| Median serum concentration (ng/g of lipid) | —              | 1.9           | 3.6           | 6.6           | 24.6          |          |             |
| Cases/n                                    | 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, BMI, cigarette smoking, serum cotinine, alcohol consumption, and exercise. †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.

showed some nonlinear trends, but none were significant.

**CONCLUSIONS**— In this article, we continued our examination of the relationships of POPs with diabetes and metabolic syndrome by studying BFRs. Among six 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 article. In our previous studies on

chlorinated POPs (1–3), most chemicals belonging to the PCB and organochlorine 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, 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 it is used as an additive to retard fire and flames in a variety of commercial and household products (14). Humans are exposed to

PBDEs in house dust in direct inhalation, ingestion, and dermal exposure (5). Unlike PBDEs, PBBs were prohibited in the U.S. in the 1970s after an accidental human exposure in Michigan (15). Thus, their main exposure route would be diet, which is similar to that for chlorinated POPs (15). These different exposure routes were reflected in the correlations among serum BFR concentrations. Serum concentrations of five chemicals belonging to PBDEs showed very strong mutual correlations, consistent with common exposure sources. However, a serum PBB-153 concentration showed, at most, weakly positive associations in comparison with 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 si-

Table 4—Adjusted odds ratio (OR) and 95% CI of prevalence of five components of metabolic syndrome by category of PBB-153 and PBDE-153\*

|  | Not detectable | Detectable    |                |               |                | P trend† | P quadratic |
|--|----------------|---------------|----------------|---------------|----------------|----------|-------------|
|  |                | <25th‡        | 25th to <50th  | 50th to <75th | ≥75th          |          |             |
| Waist circumference >102 cm in men or >88 cm 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        |
| Triglycerides ≥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, BMI, cigarette smoking, serum cotinine, alcohol consumption, and exercise. †The median serum concentration in each category is displayed. ‡P trend was calculated without a quadratic term in the model, while P quadratic was calculated including the linear term.

multaneous 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 (1–3), we also found nonlinear dose-response relations of PCBs with various outcomes, including plateaus or inverted U-shaped associations. Among various subclasses of POPs, PCBs are the subclass that has most similar structures to BFRs (5). Thus, a 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 doses) (18). Although researchers cautioned that low-dose ef-

fects cannot be extrapolated from animal studies to humans (19), our findings on PCBs, PBBs, or PBDEs suggest that this concept might also apply in the human body.

This nonlinear 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 the 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, dyslipidemia, increased gluconeogenesis, and fatty liver (8). Furthermore, dioxin-like compounds exert their effects through binding to the arylhydrocarbon receptor, which is thought

to antagonize 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 with 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 POP 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 POP 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, the current findings 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 previously (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 the general population. Prospective studies of the relation of POPs with diabetes and metabolic syndrome are 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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#### References

- Lee DH, Lee IK, Song K, Steffes M, Toscano W, Baker BA, Jacobs DR Jr: A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999–2002. *Diabetes Care* 29:1638–1644, 2006
- Lee DH, Lee IK, Steffes M, Jacobs DR Jr: Extended analyses of the association between serum concentrations of persistent organic pollutants and diabetes. *Diabetes Care* 30:1596–1598, 2007
- Lee DH, Lee IK, Porta M, Steffes M, Jacobs DR Jr: Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999–2002. *Diabetologia* 50:1841–1851, 2007
- Lee DH, Steffes MW, Jacobs DR Jr: Can persistent organic pollutants explain the association between serum gamma-glutamyltransferase and type 2 diabetes? *Diabetologia* 51:402–407, 2008
- Lorber M: Exposure of Americans to polybrominated diphenyl ethers. *J Expo Sci Environ Epidemiol* 18:2–19, 2008
- Langford K, Scrimshaw M, Lester J: The impact of process variables on the removal of PBDEs and NPEOs during simulated activated sludge treatment. *Arch Environ Contam Toxicol* 53:1–7, 2007
- Hoppe AA, Carey GB: Polybrominated diphenyl ethers as endocrine disruptors of adipocyte metabolism. *Obesity (Silver Spring)* 15:2942–2950, 2007
- Jones OAH, Maguire ML, Griffin JL: Environmental pollution and diabetes: a neglected association. *Lancet* 371:287–288, 2008
- Remillard RBJ, Bunce NJ: Linking dioxins to diabetes: epidemiology and biologic plausibility. *Environ Health Perspect* 110:853–858, 2002
- Third National Report on Human Exposure to Environmental Chemicals [article online], 2005. Available from <http://www.cdc.gov/exposurereport/report.htm>. Accessed 11 April 2007
- Introduction to NHANES [article online], 2003. Available from [http://www.cdc.gov/nchs/about/major/nhanes/intro\\_mec.htm](http://www.cdc.gov/nchs/about/major/nhanes/intro_mec.htm). Accessed 11 May 2007
- Korn EL, Graubard BI: Epidemiologic studies utilizing surveys: accounting for the sampling design. *Am J Public Health* 81:1166–1173, 1991
- Bocio A, Llobet JM, Domingo JL, Corbella J, Teixidó A, Casas C: Polybrominated diphenyl ethers (PBDEs) in foodstuffs: human exposure through the diet. *J Agric Food Chem* 51:3191–3195, 2003
- Wu N, Herrmann T, Paepke O, Tickner J, Hale R, Harvey LE, La Guardia M, McClean MD, Webster TF: Human exposure to PBDEs: associations of PBDE body burdens with food consumption and house dust concentrations. *Environ Sci Technol* 41:1584–1589, 2007
- Fries GF: The PBB episode in Michigan: an overall appraisal. *Crit Rev Toxicol* 16:105–156, 1985
- Sjödin A, Jones RS, Focant JF, Lapeza C, Wang RY, McGahee EE 3rd, Zhang Y, Turner WE, Slazyk B, Needham LL, Patterson DG Jr: Retrospective time-trend study of polybrominated diphenyl ether and polybrominated and polychlorinated biphenyl levels in human serum from the United States. *Environ Health Perspect* 112:654–658, 2004
- Sanzgiri UY, Srivatsan V, Muralidhara S, Dallas CE, Bruckner JV: Uptake, distribution, and elimination of carbon tetrachloride in rat tissues following inhalation and ingestion exposures. *Toxicol Appl Pharmacol* 143:120–129, 1997
- Welshons WV, Nagel SC, vom Saal FS: Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. *Endocrinology* 147 (Suppl. 6):S56–S69, 2006
- Kamrin MA: The “low dose” hypothesis: validity and implications for human risk. *Int J Toxicol* 26:13–23, 2007
- Vasiliu O, Cameron L, Gardiner J, Deguire P, Karmaus W: Polybrominated biphenyls, polychlorinated biphenyls, body weight, and incidence of adult-onset diabetes mellitus. *Epidemiology* 17:352–359, 2006
- Lee DH, Jacobs DR Jr, Porta M: Could low-level background exposure to persistent organic pollutants contribute to the social burden of type 2 diabetes? *J Epidemiol Community Health* 60:1006–1008, 2006
- Grün F, Blumberg B: Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. *Endocrinology* 147 (Suppl. 6):S50–S55, 2006