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Association between Serum Concentrations of Persistent Organic Pollutants and Self-reported Cardiovascular Disease Prevalence: Results from the National Health and Nutrition Examination Survey 1999-2002

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Abbreviation

AhR: Aryl hydrocarbon receptor

CDC: Centers for Disease Control and Prevention

CHD: Coronary heart disease

CVD: Cardiovascular diseases

HCB: Hexachlorobenzene

LOD: Limit of detection

NCHS: National Center for Health Statistics

NHANES: National Health and Nutrition Examination Survey

OC pesticides: Organochlorine pesticides

ORs: Odds ratios

PCBs: Polychlorinated biphenyls

PCDDs: Polychlorinated dibenzo-p-dioxins

PCDFs: Polychlorinated dibenzofurans

POPs: Persistent Organic Pollutants

TCDD: Tetrachlorodibenzo-p-dioxin

TEF: Toxic equivalent factor

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Abstract

BACKGROUND: There is now increasing evidence that exposure to Persistent Organic Pollutants (POPs) can contribute to the development of inflammatory diseases such as atherosclerosis.

OBJECTIVE: To examine associations of serum concentrations of POPs with self-reported history of cardiovascular disease (CVD).

DESIGN: Cross-sectional associations of serum POPs concentrations with the prevalence of self-reported CVD were investigated in 889 adults aged ≥ 40 in the National Health and Nutrition Examination Survey 1999-2002. Twenty one POPs (3 polychlorinated dibenzo-*p*-dioxins (PCDDs), 3 polychlorinated dibenzofurans (PCDFs), 5 dioxin-like polychlorinated biphenyls (PCBs), 6 non-dioxin-like PCBs, 4 organochlorine pesticides (OC pesticides)) were selected, because they were detectable in ≥60% of participants.

RESULTS: Dioxin-like PCBs, non-dioxin-like PCBs, and OC pesticides were positively associated with the prevalence of CVD only among women. Compared with those in the lowest quartile of serum concentration, the odds ratios for CVD across increasing quartiles were, for dioxin-like PCBs, 0.9, 2.0, and 5.0 (P for trend<0.01), for non-dioxin-like PCBs, 1.2, 1.2, and 3.8 (P for trend<0.01), and, for OC pesticides, 1.9, 1.7, and 4.0 (P for trend=0.03). PCDDs showed positive trends with the prevalence of CVD in both men and women; adjusted odds ratios were 1.4, 1.7, and 1.9 (P for trend=0.07, men and women combined).

CONCLUSIONS: Our findings need to be carefully interpreted due to the cross-sectional design and use of self-reported CVD. Prospective studies are needed to clarify these associations.

Introduction

Persistent organic pollutants (POPs) are a family of lipophilic stable chemicals that bioaccumulate in adipose tissue and create a lasting toxic body burden (Van den Berg et al. 2006). In addition to various known deleterious effects, POPs have recently been implicated as a possible cause of cardiovascular diseases (CVD) (Mastin 2005). The association between POPs and CVD is plausibly causal through several biological mechanisms. Exposure to polychlorinated biphenyls (PCBs) or 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is known to increase atherogenic serum lipid levels in both animals and humans (Bombick et al. 1984; Lovati et al. 1984; Swift et al. 1981). In addition, these contaminants cause direct damage to endothelial cells via oxidative stress (Hennig et al. 2002; Stegeman et al. 1995; Toborek et al. 1995). Combination of an elevation in serum lipids with damage to endothelial cells would be expected to increase the risk of CVD. There is also epidemiological evidence for the association of POPs with CVD, though it is not totally consistent. Weakly or modestly elevated rate ratios for mortality from ischemic heart disease were found in several cohorts, in which there was occupational or accidental relatively brief exposure to high doses of several POPs (Bertazzi et al. 1998, 2001; Calvert et al. 1998; Gustavsson and Hogstedt 1997; Hooiveld et al. 1998; Pesatori et al. 1998, 2003; Steenland et al. 1999; Vena et al. 1998). One recent study reported that residents living in ZIP codes contaminated with POPs had a statistically significant elevation in both coronary heart disease (CHD) and acute myocardial infarction hospital discharge rates compared with clean ZIP codes (Sergeev and Carpenter 2005).

There is ongoing controversy concerning health effects of background, enduring environmental exposure to endocrine disruptors such as POPs (Kaiser 2000). There is a need for epidemiological study in the general population because extrapolation from studies of high

exposure to selected POPs in occupational or accidental settings may not appropriate to background exposure (Lee et al. 2006a). In support of this assertion, we recently reported a striking dose-response relation between serum concentrations of POPs and diabetes in the general population with background exposure to POPs (Lee et al. 2006b).

Serum concentrations of biologically important POPs or their metabolites, including dioxins and furans (polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs)), PCBs, hexachlorobenzene (HCB), and several organochlorines used as pesticides (OC pesticides), were measured in subsamples of the National Health and Nutrition Examination Survey (NHANES) 1999-2000 and 2001-2002 (NCHS 2005). This study was performed to investigate associations of prevalent self-reported CVD with the serum concentrations of POPs, restricting to those POPs that were widely prevalent to ensure a valid CVD prevalence estimate in the referent group with low exposure.

Methods

The 1999-2000 and 2001-2002 NHANES conducted by the Centers for Disease Control and Prevention were designed to be nationally representative of the noninstitutionalized, U.S. civilian population on the basis of a complex, multistage probability sample. Approximately 9965 persons, aged 2 months to 85 yr were studied in NHANES 1999-2000, and 11,039 persons in NHANES 2001-2002. Details of the NHANES protocol and all testing procedures are available elsewhere (NCHS 2006a, 2006b). The study protocol was reviewed and approved by the CDC institutional review board; additionally, informed written consent was obtained from all subjects before they took part in the study.

PCDDs, PCDFs, PCBs, and OC pesticides were measured in serum from a random one-third subsample of people aged 12 years and older in 1999 and 2000. In 2001 and 2002, PCDDs, PCDFs, and coplanar PCBs were measured in a random one-third subsample of

people aged 20 years and older and OC pesticides and other PCBs were measured in these people and in a random one-third subsample of people aged 12-19 years and older.

The NHANES data collection included a standardized home interview followed by a detailed physical examination in a mobile evaluation clinic or the participant's home. Information on demographic characteristics, ethnicity, and medical history of diabetes was obtained in a household interview. Venous blood and urine samples were collected and shipped weekly at -20°C. PCDDs, PCDFs, PCBs, and OC pesticides were all measured as individual chemicals by high-resolution gas chromatography/high-resolution mass spectrometry using isotope dilution for quantification. All of these analytes were measured in approximately 5mL of serum using a modification of the method of Turner et al (1997). The POPs were reported on a lipid adjusted basis using concentrations of serum total cholesterol and triglycerides.

Although 49 POPs were measured in both NHANES 1999-2000 and 2001-2002, to avoid bias in estimation among those below the limit of detection (LOD), we selected the 21 POPs for which at least 60% of study subjects had concentrations more than the LOD; 3 polychlorinated dibenzo-*p*-dioxins (PCDDs), 3 polychlorinated dibenzofurans (PCDFs), 5 dioxin-like PCBs, 6 non-dioxin-like PCBs, and 4 OC pesticides. There were a total of 1,054 study participants aged 40 years and older with information on serum concentrations of the 21 selected POPs. After excluding 165 diabetic participants including newly-diagnosed cases, the final sample size was 889. We excluded those with diabetes from the current study because simple adjustment for diabetic status may not be enough to exclude its effect due to strong associations between serum concentrations of POPs and diabetes (Lee et al, 2006b). However, inclusion of diabetic patients did not materially change results.

For each POP, subjects with serum concentrations under LOD were regarded as the

reference group, and subjects with detectable values categorized by cutoff points of 25th, 50th, and 75th percentile values. To yield a cumulative measure of 3 PCDDs, we summed the ranks according to magnitude of detectable levels of the 3 POPs which belong to the PCDDs, using the rank 0 for any nondetectable value. The summary values were categorized by cutoff points of 25th, 50th, and 75th percentile values. We assigned and cumulated POP subclasses similarly for the 3 PCDFs, the 5 dioxin-like PCBs, the 6 non-dioxin-like PCBs and the 4 OC pesticides. Thus, depending on the sum of ranks of the several POPs belonging to the specific POP sub-class under consideration, the subject could be in the lowest quartile or in a higher quartile; however, if all POPs in the subclass were nondetectable, the subject would be placed in the lowest quartile.

Participants were considered to have prevalent CVD if they answered "yes" to any of the following questions; "Has a doctor or other health professional ever told you that you had CHD?", "Has a doctor or other health professional ever told you that you had angina/angina pectoris?", "Has a doctor or other health professional ever told you that you had heart attack/myocardial infarction?", or "Has a doctor or other health professional ever told you that you had a stroke?" Logistic regression models were used to calculate multivariate-adjusted odds ratios (ORs). Adjusting CVD risk factors were age (years), race/ethnicity, poverty income ratio (continuous), body mass index (continuous), cigarette smoking (never, former, or current), cotinine levels (ng/ml), alcohol consumption (g/day), and leisure time physical activity (vigorous, moderate, or none), status of hypertension (yes/no), total cholesterol (continuous), HDL-cholesterol (continuous), triglyceride (continuous), and C-reactive protein (continuous). We substituted median values of noncases for missing body mass index, poverty income ratio, cotinine levels, or alcohol consumption in 152 subjects; exclusion of these individuals did not change any conclusions, but did limit power in some analyses, so they

were retained.

All statistical analyses were performed with SAS 9.1 (SAS Institute, Cary, NC) and SUDAAN 9.0 (Research Triangle Institute, Research Triangle Park, NC). Estimates of main results were calculated accounting for stratification and clustering (Korn and Graubard 1991), adjusting for age, race and ethnicity, and poverty income ratio instead of using sample weights; this adjustment is regarded as a good compromise between efficiency and bias (Graubard and Korn 1999; Korn and Graubard 1991). As results were very similar with SAS 9.1 and SUDAAN 9.0, we here presented the results based on SAS 9.1.

Results

The sample of 889 participants included 48% men and 55% whites. Mean ± standard deviation for age was 60.4 ± 13.6 years (range 40-85). In Table 1, we presented associations of known CVD risk factors with 5 subclasses of POPs, rather than the 21 specific POPs, as our final conclusion was made based on the results of these 5 subclasses. Age was the strongest and most important correlate of serum concentrations of all 5 subclasses of POPs in both genders. However, associations of other CVD risk factors with POPs appeared to be substantially different depending on specific classes of POPs. Subjects with white race had lower concentrations of OC pesticides in both genders and PCDDs in women, but higher PCDFs or PCBs especially among women. Those with greater income had higher concentrations of PCBs, but lower OC pesticides. Obese people tended toward higher concentrations of most POPs, except non-dioxin-like PCBs among women. Smokers tended to have lower concentrations of some POPs while drinkers had higher concentrations of PCBs. HDL-cholesterol, total cholesterol, and triglycerides were variously associated depending on subclasses of POPs or gender. HDL-cholesterol was positively associated with PCBs, but inversely with OC pesticides. As the serum concentrations of POPs used in this study were

already adjusted for both total cholesterol and triglyceride, most of POPs were not associated or were even inversely associated with total cholesterol or triglycerides, except positive associations between OC pesticides with triglycerides. When lipid-unadjusted POPs levels were used, all 5 subclasses of POPs were positively associated with both total cholesterol and triglycerides (data not shown). C-reactive protein was positively associated with OC pesticides in both genders, but inversely with non-dioxin-like PCBs among women. After adjusting for age, there were positive pairwise correlations among serum concentrations of the 5 subclasses of POPs with correlation coefficients from 0.32 to 0.84 in men and 0.28 to 0.86 in women.

There were 108 prevalent self-report CVD cases (61 men and 47 women). They consisted of 87 CHD (sum of CHD, angina, and heart attack) and 40 stroke cases; some persons reported more than one condition. Table 2 shows associations between 5 sub-classes of POPs and the prevalence of CVD by gender. PCDDs showed positive trends with the prevalence of CVD in both men and women even though stratified analyses by gender failed to reach statistical significances. When both genders were combined, the adjusted ORs were 1.4, 1.7, and 1.9 (P for trend=0.07). PCDFs were unassociated with the prevalence of CVD in either gender. Dioxin-like PCBs, non-dioxin like PCBs, and OC pesticides showed significantly positive associations with the prevalence of CVD only among women; adjusted odds ratios across quartiles of each sub-classes were 0.9, 2.0, and 5.0 (P for trend<0.01), 1.2, 1.2, and 3.8 (P for trend<0.01), and 1.9, 1.7, and 4.0 (P for trend=0.03), respectively. In the fully adjusted models, serum levels of HDL-cholesterol, total cholesterol, and triglycerides were included to eliminate residual confounding, even though lipid adjusted POPs concentrations were used. However, dropping individual lipids from the list of covariates did not change results.

In Tables 3 and 4, we further examined associations of prevalence of CVD with specific POPs belonging to sub-classes which showed positive associations in Table 2. In the case of PCDDs, we presented the results in both men and women (Table 3). Among 3 POPs belonging to PCDDs, only 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin showed significant trends in both men and women. Even though 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin and 1,2,3,4,6,7,8,9-octachlorodibenzo-p-dioxin did not show linear trends, the risk appeared to substantially increase from the 1st or 2nd category of detectable range compared with nondetectable value, especially in men. On the other hand, most POPs belonging to dioxin-like PCBs, non-dioxin like PCBs, and OC pesticides showed dose-response relations with CVD in women (Table 4).

In all analyses, we further considered self-reported weight loss in the past 1 or 10 years as possible confounders because weight loss increases serum concentrations of POPs and patients with a history of CVD may intentionally decrease their body weight after diagnosis. However, the adjustment for weight loss did not change the results (data not shown). When the dataset was reanalyzed using the 87 CHD cases as the outcome variable, the trends were very similar with those of CVD cases (data not shown).

Discussion

This cross-sectional study demonstrated that the background exposure to POPs was positively associated with the prevalence of CVD in the U.S. general population. Details of associations were substantially different depending on specific sub-classes of POPs or gender, but the associations with CVD suggested by the data would be as strong as those of traditional CVD risk factors.

Our findings are in general agreement with, but stronger than those of previous prospective cohort studies among subjects exposed to high concentrations of selected POPs in

occupational or accidental settings (Bertazzi et al. 1998, 2001; Calvert et al. 1998; Gustavsson and Hogstedt 1997; Hooiveld et al. 1998; Pesatori et al. 1998, 2003; Steenland et al, 1999; Vena et al, 1998). Considering that exposure levels in this study were much lower than those in previous studies, this may be a puzzling finding. Interestingly, we also reported striking dose-response relations between serum concentrations of POPs and prevalent diabetes in the same NHANES dataset (Lee et al. 2006b). In a recent editorial (Lee et al. 2006a), we discussed that epidemiological studies in general populations who are neither occupationally nor accidentally exposed may be critical to investigate possible health effects of POPs in humans. Specifically, previous studies often failed to select a true reference group with very low exposure levels to POPs, for example by examining people with very low serum concentrations of POPs, despite persistence of the POPs in adipose tissue and consistent background environmental exposure to them. They generally did not examine the possibility that a mixture of POPs could have an additive or synergistic effect on health, as we have done by employing a summary measure that considered joint health effects of POPs with possibly different toxicological properties. They did not consider the possibility of nonlinear associations. All of these points can lead to substantial underestimation of risk or masking of true risk.

On the other hand, the fact that CVD was associated with various POPs with different toxicological profiles may be also consistent with the possibility that the observed relations are not causal. It is entirely possible that the POPs studied in this study are not themselves causally related to CVD. Rather, they could be surrogates of exposure to a mixture of POPs in the general population because there are high correlations among serum concentrations of various POPs in the human body. Furthermore, we can not completely exclude the possibility of reverse causality; CVD diseases may alter metabolism so as to increase serum

concentrations of POPs. However, if reverse causality were occurring, it would be sensible to expect that all POPs in both sex would be associated with CVD, rather than selected POPs as we observed.

The NHANES data provided a unique chance to investigate the possible associations between serum concentrations of various POPs and CVD in a random sample of the general population, despite the recognition that self-reported CVD as the dependent variable is less accurate than physician-diagnosed CVD. Previous epidemiological studies have focused on selected populations, often occupationally or accidentally exposed to high levels of selected POPs.

In this study, the specific sub-classes of POPs related to CVD appeared to differ by gender. Serum concentrations of PCDDs were positively associated with prevalence of CVD among men, but women showed strong positive associations with dioxin-like or non-dioxin-like PCBs or OC pesticides. It is well-known that men and women differ in many aspects of vulnerability to environmental xenobiotics and other stressors (Gochfeld 2006). Gender differences in the response of nonreproductive cells, in addition to reproductive cells, to TCDD or PCBs have been observed in several animal studies (Enan et al. 1996; Vega-Lopez et al. 2007; Wyde et al. 2001). As most occupational epidemiological studies on POPs have been performed among men, it is largely unknown whether various health effects of POPs between men and women are similar or not. In our previous study of diabetes (Lee et al. 2006b), the associations of POPs did not differ between genders.

There is increasing experimental evidence that exposure to POPs such as TCDD or PCBs can lead to cardiovascular toxicity and atherosclerosis. A number of biochemical changes induced by POPs observed in *in vitro* or *in vivo* experimental studies are viewed as atherogenic. PCBs or TCDD can compromise the normal function of vascular endothelial

cells by activating oxidative stress-sensitive signaling pathways and subsequent proinflammatory events critical in the pathology of atherosclerosis and CVD (Hennig et al. 2002; Stegeman et al. 1995; Toborek et al. 1995). In addition, exposure to TCDD increased serum cholesterol, triglyceride, and phospholipids and suppressed low density lipoprotein receptors in the liver (Bombick et al. 1984; Lovati et al. 1984; Swift et al. 1981). Moreover, TCDD promoted the differentiation of macrophages to atherogenic foam cells or deregulated several genes in cell proliferation and apoptosis in smooth muscle cell (Dalton et al. 2001; Vogel et al. 2004).

Unlike evidence from experimental studies in which the affinity to aryl hydrocarbon (AhR) was important to induce atherosclerosis (Hennig et al. 2002; Stegeman et al. 1995; Toborek et al. 1995), the strengths of association of each POP belonging to the category of PCDDs or PCDFs did not appear to be correlated with the toxic equivalent factors (TEFs) of each POP; The concept of TEFs, a measure of the ability to bind to the AhR, has been developed to facilitate risk assessment and regulatory control of exposure to complex PCDD, PCDF and PCB mixtures (Van den Berg et al. 2006). Also, non-dioxin-like PCBs appeared to show more consistent and stronger associations than dioxin-like PCBs. Even among the dioxin-like PCBs, PCBs with low TEFs tended to show stronger associations than those with high TEFs. Our previous study of the associations between POPs and diabetes similarly reported no relation between strength of association and TEF of each POP (Lee DH et al. 2006b).[19] These findings suggest that the affinity to AhR may not be a critical pathway of toxicity of POPs in human for some outcomes, unlike findings from cells or animal models. Alternatively, the associations of some POPs with CVD observed in this study may not be direct as we discussed above.

This study has several limitations, primarily its cross-sectional design, but also that

diagnosis of CVD was self-report and fatal events were not even considered. The expense and blood volume needed to measure POPs in a population sample are such that such data are rare and the NHANES data therefore may offer important insights, despite these limitations. In the case of misdiagnosis, we expect that the misclassification would be nondifferential, leading to the underestimation of ORs. Misclassification bias is also possible because some subjects with a higher value of POP but a lower sample volume could be classified in the reference group, or vice versa. Such misclassification is also likely to be nondifferential, because sample volume is probably unrelated to prevalence of CVD.

In summary, there were positive associations between serum concentrations of some POPs and prevalence of CVD in this sample of the U.S. population. Thus, prospective study of the relation between background dioxin exposure and validated CVD should be a priority in further study of these associations. Both the exposure and the disease have substantial prevalence and the public health significance of a causal relation of POPs with CVD could be marked.

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Table 1. Age-adjusted Spearman correlation coefficients [a] between 5 categories of lipid-adjusted persistent organic pollutants with demographic or cardiovascular risk factors by gender

	Polychlorinated dibenzo-p-dioxins	Polychlorinated dibenzofurans	Dioxin-like polychlorinated biphenyl	Non-dioxin-like polychlorinated biphenyl	Organochlorine pesticides
Men					
Age	+0.39**	+0.23**	+0.48**	+0.44**	+0.47**
Race	NS	NS	NS	NS	-0.20**
Poverty income ratio	NS	NS	+0.14**	NS	NS
Body mass index	+0.21**	+0.10*	+0.10*	NS	+0.20**
Current smoker	-0.16**	NS	-0.12*	NS	NS
Exercise	NS	NS	NS	NS	-0.11*
Alcohol consumption	NS	NS	+0.11*	+0.10*	NS
HDL-cholesterol	NS	NS	NS	+0.14**	NS
Total cholesterol	NS	NS	NS	NS	NS
Triglycerides	NS	NS	NS	NS	+0.18**
C-reactive protein	NS	NS	NS	NS	+0.11*
Women					
Age	+0.42**	+0.36**	+0.62**	+0.51**	+0.57**
Race	NS	+0.10*	+0.10*	NS	-0.30**
Poverty income ratio	NS	NS	+0.10*	+0.10*	-0.18**
Body mass index	+0.10*	NS	NS	-0.14**	+0.19**
Current smoker	-0.25**	-0.10*	NS	NS	NS
Exercise	NS	NS	NS	NS	NS
Alcohol consumption	NS	NS	NS	NS	NS
HDL-cholesterol	NS	NS	+0.10*	+0.12**	-0.17**
Total cholesterol	NS	-0.15**	-0.09*	NS	NS
Triglycerides	NS	-0.10*	NS	-0.13**	+0.16**
C-reactive protein	NS	NS	NS	-0.10*	+0.15**

NS, not significant, For race, white=1, and others=0, For current smoker, current=1, and others=0. For exercise, yes=1, and no=0

[a] : Before calculating correlation coefficients, detectable values of each POP were individually ranked and the rank order of the individual POPs in each subclass were summed to arrive at the subclass value. All not detectable values were ranked as 0.

*: $P<0.05$, **: $P<0.01$

Table 2 Adjusted[a] odds ratio (OR) and 95% confidence interval (CI) of prevalence of cardiovascular diseases by quartiles[b] of polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), dioxin-like polychlorinated biphenyls (PCBs), non-dioxin-like PCBs, and organochlorine (OC) pesticides in men and women[†]

Analyte		<25th†	25th-<50th	50th-<75th	≥75th	P_{trend}
Men						
PCDDs	Cases/no.	7/106	12/107	19/107	23/107	
	Adjusted OR (95% CI)	Referent	1.7 (0.6-4.7)	2.1 (0.8-5.9)	2.2 (0.8-6.1)	0.14
PCDFs	Cases/no.	13/106	12/107	17/107	19/107	
	Adjusted OR (95% CI)	Referent	0.7 (0.3-1.8)	0.9 (0.4-2.2)	0.7 (0.3-1.7)	0.60
Dioxin-like PCBs	Cases/no.	6/106	16/107	17/107	22/107	
	Adjusted OR (95% CI)	Referent	2.2 (0.8-6.5)	1.8 (0.6-5.3)	1.7 (0.6-5.5)	0.64
Non-dioxin like PCBs	Cases/no.	7/106	17/107	14/107	23/107	
	Adjusted OR (95% CI)	Referent	2.3 (0.8-6.4)	1.3 (0.5-3.9)	1.8 (0.6-5.0)	0.61
OC pesticides	Cases/no.	10/106	12/107	18/108	21/106	
	Adjusted OR (95% CI)	Referent	0.7 (0.2-1.9)	0.9 (0.3-2.4)	0.9 (0.3-2.3)	0.96
Women						
PCDDs	Cases/no.	8/115	9/116	11/116	19/115	
	Adjusted OR (95% CI)	Referent	1.1 (0.3-3.3)	1.5 (0.5-4.3)	2.0 (0.7-6.4)	0.16
PCDFs	Cases/no.	9/115	10/116	13/116	15/115	
	Adjusted OR (95% CI)	Referent	0.9 (0.3-2.5)	1.1 (0.4-3.0)	1.0 (0.3-2.8)	0.92
Dioxin-like PCBs	Cases/no.	4/115	8/116	12/116	23/115	
	Adjusted OR (95% CI)	Referent	0.9 (0.2-3.5)	2.0 (0.5-7.6)	5.0 (1.2-20.4)	<0.01
Non-dioxin like PCBs	Cases/no.	5/115	9/115	9/117	24/115	
	Adjusted OR (95% CI)	Referent	1.2 (0.4-4.0)	1.2 (0.4-4.2)	3.8 (1.1-12.8)	0.02
OC pesticides	Cases/no.	3/115	9/116	10/116	25/115	
	Adjusted OR (95% CI)	Referent	1.9 (0.5-7.7)	1.7 (0.4-7.1)	4.0 (1.0-17.1)	0.03

[a]Adjusted for age, race, poverty income ratio, body mass index, cigarette smoking, serum cotinine, alcohol consumption, exercise, HLD-cholesterol, total cholesterol, triglycerides, hypertension, and C-reactive protein

[b]Detectable values of each POP were individually ranked and the rank orders of the individual POPs in each subclass were summed to arrive at the subclass value. All not detectable values were ranked as 0. The summary values were categorized by cutoff points of 25th, 50th, and 75th values of the sum of ranks.

Table 3. Adjusted[a] odds ratio (OR) and 95% confidence interval (CI) of prevalence of self-reported cardiovascular diseases by category of polychlorinated dibenzo-p-dioxins (PCDDs) in men and women

Analyte	Detection Rate		Not detectable	Detectable				P_{trend}
				<25th	25th-<50th	50th-<75th	≥75th	
Men								
1,2,3,6,7,8,-Hexachlorodibenzo-p-dioxin	82.2%	Conc. (pg/g of lipid)[b]	-	26.6	42.1	61.3	111	
		Cases/no.	5/76	3/86	14/89	21/89	18/87	
		Adjusted OR	Referent	0.9	4.3	4.1	2.5	0.04
		(95% CI)		(0.2-4.0)	(1.3-14.2)	(1.3-12.6)	(0.8-7.7)	
1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin	89.5%	Conc. (pg/g of lipid)	-	20.7	40.0	61.7	111	
		Cases/no.	3/45	12/95	17/96	11/96	18/95	
		Adjusted OR	Referent	3.2	3.7	1.7	2.4	0.94
		(95% CI)		(0.8-13.3)	(0.9-15.4)	(0.4-7.6)	(0.5-10.3)	
1,2,3,4,6,7,8,9-octachlorodibenzo-p-dioxin	82.0%	Conc. (pg/g of lipid)	-	192	310	469	899	
		Cases/no.	4/77	7/87	18/88	16/88	16/87	
		Adjusted OR	Referent	1.5	3.7	2.7	2.1	0.28
		(95% CI)		(0.4-6.0)	(1.1-12.6)	(0.8-9.6)	(0.6-7.7)	
Women								
1,2,3,6,7,8,-Hexachlorodibenzo-p-dioxin	83.8%	Conc. (pg/g of lipid)	-	27.6	45.9	66.1	111	
		Cases/no.	6/75	5/96	3/97	12/97	21/97	
		Adjusted OR	Referent	1.0	0.4	1.7	2.8	0.04
		(95% CI)		(0.3-3.7)	(0.1-1.9)	(0.5-5.2)	(0.9-8.6)	
1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin	93.1%	Conc. (pg/g of lipid)	-	25.5	50.2	76.6	135	
		Cases/no.	3/32	12/107	7/108	11/108	14/107	
		Adjusted OR	Referent	1.6	1.3	2.2	1.9	0.45
		(95% CI)		(0.3-7.9)	(0.2-7.7)	(0.4-12.0)	(0.3-10.8)	
1,2,3,4,6,7,8,9-octachlorodibenzo-p-dioxin	92.9%	Conc. (pg/g of lipid)	-	278	445	660	1170	
		Cases/no.	4/33	10/107	4/107	12/108	17/107	
		Adjusted OR	Referent	0.6	0.2	0.7	0.7	0.74
		(95% CI)		(0.1-2.4)	(0.1-1.1)	(0.2-2.7)	(0.2-2.8)	

[a]Adjusted for age, race, poverty income ratio, body mass index, cigarette smoking, serum cotinine, alcohol consumption, exercise, HLD-cholesterol, total cholesterol, triglycerides, hypertension, and C-reactive protein

[b]Median values were displayed in each category

Table 4. Adjusted[a] odds ratio (OR) and 95% confidence interval (CI) of prevalence of cardiovascular diseases by categories of specific persistent organic pollutants (POPs) belonging to dioxin-like polychlorinated biphenyls (PCBs), non-dioxin-like PCBs, and organochloride (OC) pesticides in women

Analyte	Detection Rate		Not detectable	Detectable				P_{trend}
				<25th†	25th-<50th	50th-<75th	≥75th	
Dioxin-like PCBs								
2,4,4',5-Tetrachlorobiphenyl (PCB74)	87.2%	Conc. (ng/g of lipid)[b]	-	8.2	13.9	20.5	36.1	
		Cases/no.	2/59	6/100	8/101	8/101	23/101	
		Adjusted OR (95% CI)	Referent	1.1 (0.2-6.1)	1.2 (0.2-6.4)	1.3 (0.2-7.3)	4.5 (0.8-24.8)	0.01
2,3',4,4',5-Pentachlorobiphenyl (PCB118)	87.7%	Conc. (ng/g of lipid)	-	8.6	15.2	26.4	49.3	
		Cases/no.	2/57	9/98	5/105	8/101	23/101	
		Adjusted OR (95% CI)	Referent	1.8 (0.3-9.4)	0.6 (0.1-4.1)	1.3 (0.2-7.8)	4.5 (0.8-25.5)	0.02
3,3',4,4',5-Pentachlorobiphenyl (PCB126)	88.1%	Conc. (ng/g of lipid)	-	18.3	31.6	51.0	95.4	
		Cases/no.	3/55	9/101	7/102	11/102	17/102	
		Adjusted OR (95% CI)	Referent	1.3 (0.3-5.8)	1.4 (0.3-6.6)	1.6 (0.4-7.4)	2.6 (0.6-12.2)	0.17
2,3,3',4,4',5-Hexachlorobiphenyl (PCB156)	71.4%	Conc. (ng/g of lipid)	-	5.9	9.0	12.1	20.9	
		Cases/no.	3/132	5/83	7/83	15/81	17/83	
		Adjusted OR (95% CI)	Referent	2.0 (0.4-9.5)	2.6 (0.6-12.0)	9.2 (2.1-39.4)	10.4 (2.3-46.7)	<0.01
3,3',4,4',5,5'-Hexachlorobiphenyl (PCB169)	89.6%	Conc. (ng/g of lipid)	-	13.3	21.7	32.4	51.0	
		Cases/no.	3/48	5/103	8/104	16/103	15/104	
		Adjusted OR (95% CI)	Referent	0.6 (0.1-2.7)	0.9 (0.2-3.9)	1.2 (0.3-5.3)	1.2 (0.3-5.1)	0.38
Non-dioxin like PCBs								
2,2',4,4'5-Pentachlorobiphenyl (PCB99)	74.2%	Conc. (ng/g of lipid)	-	6.0	9.7	14.5	26.9	
		Cases/no.	10/119	4/84	3/87	12/86	18/86	
		Adjusted OR (95% CI)	Referent	0.3 (0.1-1.1)	0.2 (0.1-1.0)	1.1 (0.4-3.0)	1.5 (0.5-3.9)	0.08
2,2',3,4,4',5-Hexachlorobiphenyl (PCB138)	87.7%	Conc. (ng/g of lipid)	-	18.3	32.1	51.3	91.0	
		Cases/no.	1/57	10/100	4/102	7/102	25/101	
		Adjusted OR (95% CI)	Referent	6.8 (0.8-58.9)	1.6 (0.2-15.9)	3.6 (0.4-32.8)	13.4 (1.6-115.0)	<0.01
2,2',4,4',5,5'-Hexachlorobiphenyl (PCB153)	90.3%	Conc. (ng/g of lipid)	-	27.3	48.5	71.8	127.0	
		Cases/no.	1/45	7/104	8/105	9/103	22/105	
		Adjusted OR (95% CI)	Referent	3.7 (0.4-34.8)	3.0 (0.3-27.1)	3.6 (0.4-33.5)	10.4 (1.1-94.1)	<0.01
2,2',3,3',4,4',5-Heptachlorobiphenyl (PCB170)	88.3%	Conc. (ng/g of lipid)	-	9.2	15.2	21.9	36.4	
		Cases/no.	1/54	5/102	11/101	10/103	20/102	
		Adjusted OR (95% CI)	Referent	2.5 (0.3-23.3)	3.8 (0.4-33.3)	3.5 (0.4-32.1)	9.2 (1.0-84.5)	0.01

2,2',3,4,4',5,5'-Heptachlorobiphenyl (PCB180)	92.2%	Conc. (ng/g of lipid)	-	18.9	34.6	51.3	86.4	
		Cases/no.	1/36	6/107	10/106	10/107	20/106	
		Adjusted OR (95% CI)	Referent	1.8 (0.2-16.5)	2.0 (0.2-17.9)	2.0 (0.2-18.7)	4.5 (0.5-40.9)	0.07
2,2',3,4',5,5',6-Heptachlorobiphenyl (PCB187)	82.5%	Conc. (ng/g of lipid)	-	7.4	11.2	16.8	30.4	
		Cases/no.	1/86	8/93	9/98	12/95	17/95	
		Adjusted OR (95% CI)	Referent	5.0 (0.6-43.5)	3.5 (0.4-30.2)	5.8 (0.7-50.1)	7.4 (0.9-63.6)	0.07
OC pesticides								
p,p'-Dichlorodiphenyltrichloroethane	100%	Conc. (ng/g of lipid)	-	189	556	1145	2440	
		Cases/no.	-	8/115	9/116	10/116	20/115	
		Adjusted OR (95% CI)		Referent	0.8 (0.3-2.9)	0.7 (0.2-2.1)	1.7 (0.6-4.9)	0.22
Oxychlordane	93.7%	Conc. (ng/g of lipid)	-	12.1	20.2	31.4	50.5	
		Cases/no.	0/29	3/108	9/108	9/110	26/107	
		Adjusted OR (95% CI)		Referent	1.9 (0.4-7.7)	1.7 (0.4-7.6)	6.8 (1.6-29.3)	<0.01
Trans-Nonachlor	98.3%	Conc. (ng/g of lipid)	-	15.4	27.2	42.4	80.8	
		Cases/no.	0/8	2/113	10/114	12/114	23/113	
		Adjusted OR (95% CI)		Referent	3.7 (0.7-18.6)	3.4 (0.7-17.1)	6.5 (1.3-33.6)	0.03
Heptachlor Epoxide	68.2%	Conc. (ng/g of lipid)	-	5.9	9.2	13.1	23.9	
		Cases/no.	9/147	1/78	8/80	13/79	16/78	
		Adjusted OR (95% CI)	Referent	0.1 (0.1-1.3)	1.1 (0.3-3.2)	2.0 (0.7-5.8)	1.9 (0.6-5.7)	0.05

[a]Adjusted for age, race, poverty income ratio, body mass index, cigarette smoking, serum cotinine, alcohol consumption, exercise, HLD-cholesterol, total cholesterol, triglycerides, hypertension, and C-reactive protein

[b]Median values were displayed in each category