Association Between Serum Concentrations of Persistent Organic Pollutants and Insulin Resistance Among Nondiabetic Adults

Results from the National Health and Nutrition Examination Survey 1999–2002

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OBJECTIVE — We reported strong relations between serum concentrations of persistent organic pollutants (POPs), especially organochlorine (OC) pesticides or nondioxin-like polychlorinated biphenyls (PCBs), and prevalence of diabetes in a U.S population with background exposure to POPs. Here, we investigated POPs and insulin resistance, a frequent pathogenic precursor of type 2 diabetes.

RESEARCH DESIGN AND METHODS — Serum POPs and homeostasis model assessment of insulin resistance (HOMA-IR) were investigated cross-sectionally in 749 nondiabetic participants aged ≥20 years. Nineteen POPs in five subclasses were selected, detectable in ≥60% of participants.

RESULTS — Among subclasses, OC pesticides were most strongly associated with HOMA-IR. Adjusted geometric means of HOMA were 3.27, 3.36, 3.48, and 3.85 (P for trend <0.01) across quartiles of OC pesticides. The relationship strengthened with increasing HOMA-IR percentile: adjusted odds ratios comparing the highest versus lowest POPs quartile were 1.8 for being ≥50th percentile of HOMA-IR, 4.4 for being ≥75th percentile, and 7.5 for being ≥90th percentile. Associations with elevated HOMA-IR appeared to be specific to oxychlordane and trans-nonachlor but also were found for two nondioxin-like PCBs. No HOMA-IR associations were seen in the other three POP subclasses. The association between OC pesticides and HOMA-IR tended to strengthen as waist circumference increased, with no apparent association in the lowest quartile of OC pesticide concentrations.

CONCLUSIONS — These findings, coupled with those concerning diabetes prevalence, suggest that OC pesticides and nondioxin-like PCBs may be associated with type 2 diabetes risk by increasing insulin resistance, and POPs may interact with obesity to increase the risk of type 2 diabetes.

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Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; LOD, limit of detection; NHANES, National Health and Nutrition Examination Survey; OC, organochlorine; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxin; PCDF, polychlorinated dibenzofurans; POP, persistant organic pollutant.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Recently, we reported striking dose-response relations between serum concentrations of persistent organic pollutants (POPs) and prevalence of diabetes in a random sample of the U.S population with background environmental exposure to POPs (1). Even though all six POPs (detectable among at least 80% of study subjects) were associated positively with diabetes, the POPs belonging to subclasses organochlorine (OC) pesticides (trans-nonachlor and oxychlordane) or nondioxin-like polychlorinated biphenyls (PCBs) (PCB153) were most strongly associated with diabetes, with odds ratios (ORs) for prevalent diabetes for those in the top decile of detectables compared with nondetectables of 11.5, 6.5, and 6.8, respectively. Furthermore, the prevalence of diabetes was quite low among subjects in the lowest category of POPs, even in subjects with BMI ≥30 kg/m^2 (1), suggesting that POPs stored in adipose tissue may contribute strongly to the pathogenesis of diabetes (2,3).

Virtually all patients with type 2 diabetes are insulin resistant (4), and increased insulin resistance normally precedes the onset of diabetes by one to two decades (5,6). Thus, if the strong associations of POPs with diabetes shown in our previous study were causal, it would be reasonable to expect similar relations between POPs and insulin resistance, even in the pre-diabetic stage, as we reported for POPs and diabetes prevalence. Thus, we investigated the relation of serum concentrations of POPs with insulin resistance among nondiabetic subjects using the same dataset as in our previous study (1).

RESEARCH DESIGN AND METHODS

— The 1999–2002 National Health and Nutrition Examination Survey (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 com-

plex, multistage probability sample. Details of the NHANES protocol and all testing procedures are available elsewhere (7,8). Serum concentrations of biologically important various POPs or their metabolites were measured in subsamples of the NHANES 1999–2002 surveys (9).

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. POPs were measured by high-resolution gas chromatography/high-resolution mass spectrometry using isotope dilution for quantification. All these analytes were measured in ~5 ml of serum using a modification of the method of Turner et al. (10). The POPs were reported on a lipid-adjusted basis using concentrations of serum total cholesterol and triglycerides. Plasma glucose was measured with a hexokinase enzymatic reference method (COBAS MIRA; Roche Diagnostics, Indianapolis, IN) and serum insulin by means of a radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden). Insulin resistance was estimated using the homeostasis model assessment (HOMA) method calculated by the following equation: (fasting insulin [mU/l] × fasting glucose [mmol/l]/22.5).

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 19 POPs for which at least 60% of study subjects had concentrations more than the LOD: three polychlorinated dibenzo-*p*-dioxins (PCDDs), three polychlorinated dibenzofurans (PCDFs), four dioxin-like PCBs, five nondioxin-like PCBs, and four OC pesticides. There were 852 study participants aged ≥20 years with information on both fasting morning samples and serum concentrations of the 19 selected POPs. After excluding 103 subjects who had diabetes, the final sample size was 749.

For each POP, subjects with serum concentrations under the LOD were regarded as the reference group and subjects with detectable values were categorized by cutoff points of 25th, 50th, and 75th percentile values. To yield a cumulative measure of three PCDDs, we summed the ranks of the three POPs that belong to the PCDDs. The summary values were categorized by cutoff points of 25th, 50th, and 75th percentile values. We assigned and cumulated POP subclasses similarly for the three PCDFs, the four dioxin-like PCBs, the five nondioxin-like PCBs, and the four OC pesticides.

In the previous study (1), we selected the six POPs that were detected among 80% of study subjects because the selection of a true reference group with truly low levels of POPs would be very important to get valid risk estimates. As all six POPs were positively associated with diabetes, we combined the ranks of the six POPs to calculate a summary marker of six POPs. However, it would be more reasonable to summarize only POPs with similar physical and chemical properties (i.e., specific POPs belonging to the same subclasses of POPs). For this purpose, we selected 19 POPs that were detected among at least 60% of study subjects and examined the associations of POPs and HOMA of insulin resistance (HOMA-IR) within five POP subclasses. As a last step, we analyzed specific POPs belonging to those subclasses of POPs that were significantly associated with HOMA-IR.

It is important to note that subjects with serum concentrations under the LOD of a specific POP do not necessarily have zero values. They were nondetectable due to limited amounts of serum used for POP measurement. If sufficient amounts of serum were used, POPs would be detectable in almost all humans. However, as it is unlikely that the amount of serum used for POP measurement differs depending on their actual serum levels of POPs, we could assume that on average true serum concentrations of POPs among subjects with nondetectable POPs were lower than those among subjects with detectable POPs.

First, the associations of categories of POPs with HOMA were analyzed using linear regression with continuous logarithmic-transformed HOMA-IR values. Next, we assessed whether HOMA-IR differences across POP categories expanded at the higher percentiles of HOMA-IR. To do this, we estimated the OR of having HOMA-IR above a series of cut points across categories of POPs. The HOMA-IR cut points considered were the 50th percentile (≥2.34), the 75th percentile (≥3.53), and the 90th percentile (≥5.06). The use of several cutoffs allowed us to look at whether the HOMA-IR/POP association got stronger as HOMA-IR increased.

Potential confounders were age, sex, race/ethnicity, poverty income ratio, BMI, waist circumference, cigarette smoking (never, former, or current), cotinine concentrations (ng/ml), alcohol consumption (g/day), and leisure time physical activity (vigorous, moderate, or none). We substituted median values of study subjects for missing poverty income ratio, BMI, waist circumference, cotinine concentrations, or alcohol consumption in 111 subjects; exclusion of these individuals did not change any conclusions.

All statistical analyses were performed with SAS 9.1 and SUDAAN 9.0. Estimates of the main results were calculated accounting for stratification and clustering (11), 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 (11,12). 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 749 participants included 46.3% men and 49.7% white. Mean ± SD for age was 48.2 ± 18.9 years (range 20–85). Age was the strongest and most important correlate of serum concentrations of all five subclasses of POPs with correlation coefficients from 0.46 to 0.76. After adjusting for age, there were positive pairwise correlations among serum concentrations of the five subclasses of POPs with correlation coefficients from 0.24 to 0.74. Men had low serum concentrations of PCDDs and dioxin-like PCBs. White subjects had lower concentrations of OC pesticides but higher concentrations of PCDFs or PCBs. Those with higher income had lower concentrations of OC pesticides but higher PCBs. Current smokers tended to have lower concentrations of most POPs. Alcohol consumption was associated positively with PCBs, while exercise was inversely associated with OC pesticides. OC pesticides were positively associated with BMI, while nondioxin-like PCBs showed an inverse association with BMI.

Within the whole sample, arithmetic means and SDs of fasting plasma glucose, insulin, and HOMA-IR were 95.0 ± 10.9 mg/dl, 12.0 ± 8.7 mU/l, and 2.86 ± 2.17 mU/l × mmol/l, respectively. Among five subclasses of POPs, only OC pesticides were strongly associated with HOMA-IR among these nondiabetic subjects (Table 1). Adjusted geometric means of HOMA-IR were 3.27, 3.36, 3.48, and 3.85 (*P* for trend <0.01) across quartiles of OC pesticides.

Table 2 shows adjusted ORs of having higher HOMA-IR associated with quartiles of five subclasses of POPs. OC pesticides were strongly associated with the increased risk for being above the 90th

Table 1—*Adjusted* geometric means and SEs of HOMA-IR by quartiles of PCDDs, PCDFs, dioxin-like PCBs, nondioxin-like PCBs, and OC pesticides*†

Analyte	Geometric means ± SEs of HOMA-IR				P_{trend}
	<25th†	25th–<50th	50th–<75th	≥75th	
PCDDs					
Model 1	3.30 ± 0.43	3.48 ± 0.43	3.49 ± 0.42	3.68 ± 0.50	0.05
Model 2	3.39 ± 0.36	3.50 ± 0.35	3.47 ± 0.34	3.59 ± 0.40	0.25
PCDFs					
Model 1	3.45 ± 0.43	3.39 ± 0.43	3.51 ± 0.42	3.59 ± 0.46	0.46
Model 2	3.44 ± 0.35	3.48 ± 0.34	3.44 ± 0.34	3.58 ± 0.37	0.37
Dioxin-like PCBs					
Model 1	3.45 ± 0.48	3.44 ± 0.43	3.46 ± 0.42	3.59 ± 0.52	0.52
Model 2	3.50 ± 0.40	3.48 ± 0.35	3.42 ± 0.34	3.54 ± 0.42	0.93
Nondioxin-like PCBs					
Model 1	3.65 ± 0.52	3.40 ± 0.43	3.54 ± 0.44	3.36 ± 0.48	0.21
Model 2	3.49 ± 0.41	3.38 ± 0.35	3.50 ± 0.36	3.57 ± 0.42	0.42
OC pesticides					
Model 1	3.13 ± 0.45	3.30 ± 0.40	3.56 ± 0.43	4.02 ± 0.58	<0.01
Model 2	3.27 ± 0.39	3.36 ± 0.33	3.48 ± 0.35	3.85 ± 0.45	<0.01

*Model 1: Adjusted for age, sex, race, and poverty income ratio. Model 2: Additional adjustment for BMI, waist circumference, cigarette smoking, serum cotinine concentration, alcohol consumption, and exercise. †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 zero. The summary values were categorized by cutoff points of 25th, 50th, and 75th values of the sum of ranks.

percentile of HOMA-IR; adjusted ORs were 1.0, 1.4, 2.9, and 7.5 (*P* for trend <0.01). Among other POPs, both PCDDs and nondioxin-like PCBs showed positive trends even though they failed to reach statistical significances. When we used lower cutoff points of HOMA-IR, such as 75th percentile or 50th percentile, only OC pesticides were significantly associated with HOMA-IR, but the strengths of associations tended to be weaker than those of 90th percentile. When all five subclasses of POPs were included in one model, only OC pesticides were significant.

Among four specific POPs belonging to OC pesticides, both oxychlordane and trans-nonachlor were most strongly associated with the risk of elevated HOMA-IR (Table 3). When we further investigated eight POPs belonging to nondioxin-like PCBs or PCDDs (which showed nonsignificant positive trends with the outcome of HOMA-IR ≥90th percentile), both PCB170 and PCB187 were significantly associated with HOMA-IR. On the other hand, three specific POPs (PCB153, 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin, and 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin) positively associated with diabetes in a previous study (1) were not significantly associated with HOMA-IR.

In all analyses, we further considered self-reported weight loss in the 1 or 10 years before examination as possible confounders because weight loss was a strong confounder in the associations between POPs and diabetes in our previous study (13). However, the adjustment for weight loss did not change the results (data not shown).

We examined the interaction between POPs and waist circumference on the risk for insulin resistance, which was motivated by an apparent interaction between POPs and BMI on the risk of prevalent diabetes in our previous study (1). Similar to those findings, Fig. 1 shows that the association between serum concentrations of OC pesticides and the risk of higher HOMA-IR tended to be stronger as waist circumference increased even though the *P* for interaction was not significant (*P* for interaction = 0.58). Interestingly, waist circumference was not associated with elevated HOMA-IR among subjects with low concentrations of OC pesticides.

CONCLUSIONS — Using a cross-sectional design, the present study found serum concentrations of OC pesticides to be strongly and positively associated with insulin resistance among nondiabetic subjects. Coupled with the findings of our previous study on the associations between POPs and diabetes (1), the current results suggest that the background environmental exposure to some POPs, especially OC pesticides, may be critically involved in the pathogenesis of diabetes through a pathway involving insulin resistance. Among several OC pesticides, both oxychlordane (metabolites of chlordane) and trans-nonachlor (impurity of chlordane) were most strongly associated with insulin resistance. On the other hand, other classes of POPs, such as PCDDs, PCDF, or PCBs, were not strongly associated with insulin resistance among nondiabetic subjects. However, when specific individual POPs were examined, some POPs belonging to nondioxin-like PCBs were associated with higher values of HOMA-IR.

In our previous study on the association between POPs and diabetes (1), we reported strong dose-response relations of diabetes with all six POPs studied, which included members of the subclasses of PCDDs, nondioxin-like PCBs, and OC pesticides. Serum concentrations of most POPs in the general population are highly correlated each other. Thus, we cautioned that the six specific POPs that were strongly associated with diabetes may not be themselves causally related to diabetes, but we thought it was likely that either these six POPs or others highly correlated with them could be causally associated with diabetes (1). Although it was not stated in our previous study (1), it is interesting to note that trans-nonachlor was most strongly associated with diabe-

Table 2—*Adjusted* ORs and 95% CIs of prevalence of elevated HOMA-IR by quartiles of PCDDs, PCDFs, dioxin-like PCBs, nondioxin-like PCBs, and OC pesticides*

Analyte	<25th†	25th–<50th	50th–<75th	≥75th	P_{trend}
>90th percentile versus lower values					
PCDDs					
Cases/*n*	13/187	18/187	17/188	26/187	
Adjusted OR (95% CI)	Referent	1.6 (0.7–3.8)	1.3 (0.5–3.3)	2.3 (0.9–6.0)	0.14
PCDFs					
Cases/*n*	13/187	20/187	17/188	24/187	
Adjusted OR (95% CI)	Referent	1.8 (0.8–4.2)	1.2 (0.5–2.8)	1.7 (0.7–4.0)	0.46
Dioxin-like PCBs					
Cases/*n*	15/186	20/188	17/188	22/187	
Adjusted OR (95% CI)	Referent	1.5 (0.7–3.4)	1.2 (0.5–3.1)	1.4 (0.5–4.1)	0.60
Nondioxin-like PCBs					
Cases/*n*	18/187	14/187	19/188	23/187	
Adjusted OR (95% CI)	Referent	1.0 (0.4–2.4)	1.5 (0.6–3.7)	2.3 (0.8–6.4)	0.10
OC pesticides					
Cases/*n*	12/187	12/188	19/187	31/187	
Adjusted OR (95% CI)	Referent	1.4 (0.5–3.6)	2.9 (1.0–8.1)	7.5 (2.3–23.9)	<0.01
>75th percentile versus lower values					
PCDDs					
Cases/*n*	45/187	43/187	44/188	55/187	
Adjusted OR (95% CI)	Referent	0.8 (0.5–1.5)	0.8 (0.4–1.5)	1.1 (0.6–2.1)	0.80
PCDFs					
Cases/*n*	47/187	41/187	48/188	51/187	
Adjusted OR (95% CI)	Referent	0.9 (0.5–1.6)	0.9 (0.5–1.6)	1.0 (0.6–1.9)	0.89
Dioxin-like PCBs					
Cases/*n*	47/186	47/188	38/188	55/187	
Adjusted OR (95% CI)	Referent	1.0 (0.6–1.8)	0.7 (0.4–1.4)	1.2 (0.6–2.6)	0.80
Nondioxin-like PCBs					
Cases/*n*	51/187	40/187	47/188	49/187	
Adjusted OR (95% CI)	Referent	0.9 (0.5–1.6)	1.0 (0.5–2.0)	1.4 (0.7–3.0)	0.33
OC pesticides					
Cases/*n*	32/187	46/188	44/187	65/187	
Adjusted OR (95% CI)	Referent	2.2 (1.1–4.2)	1.9 (0.9–3.9)	4.4 (2.0–10.1)	<0.01
>50th percentile versus lower values					
PCDDs					
Cases/*n*	86/187	96/187	99/188	94/187	
Adjusted OR (95% CI)	Referent	1.1 (0.7–1.8)	1.0 (0.6–1.8)	0.8 (0.4–1.4)	0.48
PCDFs					
Cases/*n*	90/187	84/187	103/188	98/187	
Adjusted OR (95% CI)	Referent	0.9 (0.5–1.4)	1.2 (0.7–2.0)	1.2 (0.7–2.0)	0.37
Dioxin-like PCBs					
Cases/*n*	87/186	92/188	98/188	98/187	
Adjusted OR (95% CI)	Referent	1.0 (0.6–1.7)	1.1 (0.6–1.9)	1.1 (0.6–2.1)	0.79
Nondioxin-like PCBs					
Cases/*n*	98/187	81/187	105/188	91/187	
Adjusted OR (95% CI)	Referent	0.7 (0.4–1.2)	1.1 (0.6–2.0)	1.1 (0.5–2.1)	0.66
OC pesticides					
Cases/*n*	78/187	84/188	102/187	111/187	
Adjusted OR (95% CI)	Referent	1.0 (0.6–1.7)	1.4 (0.8–2.5)	1.8 (0.9–3.6)	0.05

*Adjusted for age, sex, race, poverty income ratio, BMI, waist circumference, cigarette smoking, serum cotinine, alcohol consumption, and exercise.†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 zero. The summary values were categorized by cutoff points of 25th, 50th, and 75th values of the sum of ranks.

tes when all six POPs studied were included in one model.

Synthesizing epidemiological findings from our previous (1,13) and current studies, we hypothesize that chlordane may be the most important POP involved in the pathogenesis of type 2 diabetes by influencing insulin resistance, although there has been no experimental study on the possible biological mechanism(s). Chlordane, a mixture of >26 compounds, was used as an agricultural pesticide on home lawns and gardens and against termites (14). Chlordane was banned in the U.S. in the1980s; however,

Table 3—*Adjusted* ORs and 95% CIs of prevalence of HOMA-IR above its 90th percentile by categories of specific POPs belonging to OC pesticides, nondioxin-like PCBs, or PCDDs†*

Analyte	Nondetectable	Detectable				P_{trend}
		<25th†	25th–<50th	50th–<75th	≥75th	
OC pesticides						
Oxychlordane						
Cases/*n*	8/140	13/154	13/151	18/151	22/153	
Adjusted OR (95% CI)	Referent	2.4 (0.8–7.0)	2.0 (0.7–6.0)	5.2 (1.6–17.4)	8.7 (2.3–33.3)	<0.01
Trans-nonachlor						
Cases/*n*	4/86	15/164	12/166	17/167	26/166	
Adjusted OR (95% CI)	Referent	2.0 (0.6–7.3)	1.6 (0.4–6.1)	2.7 (0.7–10.5)	5.4 (1.3–23.1)	0.02
p,p′-dichlorodiphenyltrichloroethane						
Cases/*n*	—	15/187	12/188	25/187	22/187	
Adjusted OR (95% CI)		Referent	0.8 (0.3–1.9)	1.4 (0.6–3.3)	1.4 (0.5–3.7)	0.33
β-Hexachlorocyclohexane						
Cases/*n*	15/198	14/137	15/138	9/138	21/138	
Adjusted OR (95% CI)	Referent	1.0 (0.4–2.4)	1.4 (0.5–3.6)	0.6 (0.2–1.8)	1.7 (0.6–5.1)	0.56
Nondioxin-like PCBs						
PCB138						
Cases/*n*	20/193	9/140	10/138	19/139	16/139	
Adjusted OR (95% CI)	Referent	0.8 (0.3–2.1)	0.8 (0.3–2.1)	1.8 (0.8–4.3)	1.5 (0.6–4.0)	0.35
PCB153						
Cases/*n*	17/155	10/147	10/150	20/149	17/148	
Adjusted OR (95% CI)	Referent	0.6 (0.3–1.6)	0.7 (0.3–1.9)	1.4 (0.5–3.5)	1.5 (0.5–4.2)	0.51
PCB170						
Cases/*n*	20/253	10/123	15/124	14/124	15/125	
Adjusted OR (95% CI)	Referent	1.8 (0.7–4.6)	2.3 (0.9–6.1)	2.7 (0.9–7.8)	3.8 (1.2–11.5)	0.02
PCB180						
Cases/*n*	18/179	10/142	16/143	11/143	19/142	
Adjusted OR (95% CI)	Referent	0.9 (0.4–2.2)	1.4 (0.6–3.5)	1.1 (0.4–3.3)	2.3 (0.8–7.0)	0.24
PCB187						
Cases/*n*	22/299	9/111	15/113	10/114	18/112	
Adjusted OR (95% CI)	Referent	1.6 (0.6–4.2)	2.7 (1.0–6.9)	2.0 (0.7–5.9)	4.2 (1.5–11.7)	0.01
PCDDs						
1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin						
Cases/*n*	22/198	9/138	12/137	15/139	16/137	
Adjusted OR (95% CI)	Referent	0.7 (0.3–1.7)	1.1 (0.5–2.5)	1.3 (0.6–3.1)	1.3 (0.5–3.4)	0.57
1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin						
Cases/*n*	6/103	11/161	20/162	14/162	23/161	
Adjusted OR (95% CI)	Referent	1.3 (0.4–4.2)	2.5 (0.8–7.5)	1.5 (0.5–4.8)	2.0 (0.6–6.4)	0.30
1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin						
Cases/*n*	14/178	13/142	15/143	16/143	16/143	
Adjusted OR (95% CI)	Referent	1.2 (0.5–2.9)	1.5 (0.6–3.6)	1.4 (0.5–3.5)	1.3 (0.5–3.5)	0.53

*Adjusted for age, sex, race, poverty income ratio, BMI, waist circumference, cigarette smoking, serum cotinine, alcohol consumption, and exercise. †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 zero. The summary values were categorized by cutoff points of 25th, 50th, and 75th values of the sum of ranks.

breakdown products of chlordane still persist in the tissue of fish, birds, and mammals and are found in breast milk (15). Chlordane is rapidly metabolized in organisms into oxychlordane and γ-chlordane or into impurities such as trans-nonachlor or *cis*-nonachlor (14). Most studies focusing on temporal trends of POPs have identified a decreasing trend since severe restriction on POPs from 1970s to 1990s, but since 1990 the reduction of POPs was gradual (15,16). In addition, no reduction of chlordane was observed in some studies (16,17), and time trends of POPs are likely to vary for different POPs in different areas (18). Pesticides banned for over two decades in the U.S., such as chlordane or dichlorodiphenyl-trichloroethane, continue to be present at significant levels in the food supply (19).

In our previous study, subjects with very low concentrations of POPs, including those who were obese (1), surprisingly experienced a low prevalence of diabetes. This suggests that POPs contained in the adipose tissue interact with obesity in contributing to diabetes risk (2,3). Some of our previous findings may be criticized due to the cross-sectional design, but the lack of association between obesity and diabetes among subjects with very low concentrations of POPs is unlikely to be a cross-sectional bias. In this study, we observed a similar interaction pattern between OC pesticides and ele-

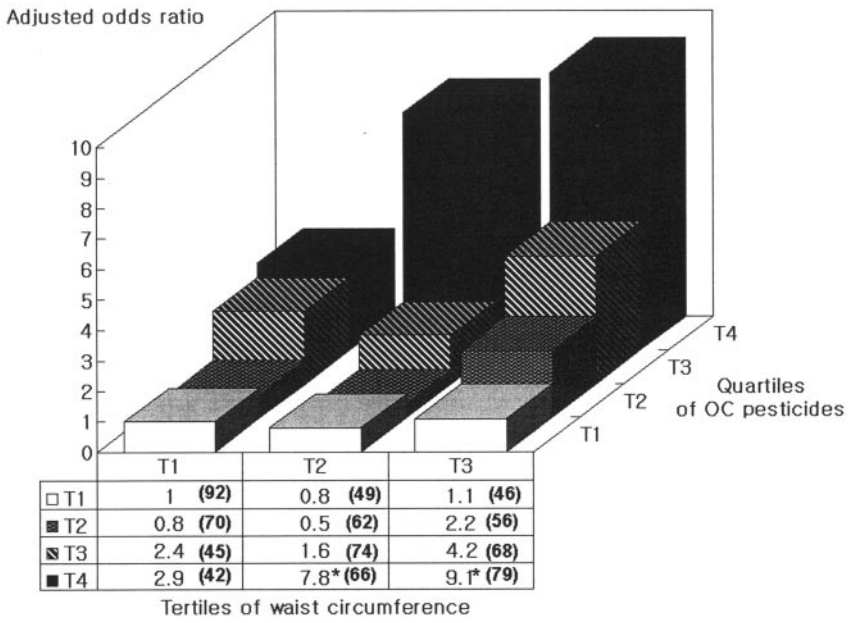

Figure 1—*Interaction between waist circumference and serum concentrations of OC pesticides on the prevalence of elevated HOMA-IR (top 10th percentile vs. lower values). Adjusted for age, sex, race, poverty income ratio, BMI, cigarette smoking, serum cotinine, alcohol consumption, and exercise (*P *for interaction = 0.58). The numbers in the table are adjusted ORs with the number at risk in each cell.* $*P < 0.05$.

vated HOMA-IR even among nondiabetic subjects. The association between serum concentration of OC pesticides and elevated HOMA-IR tended to strengthen as waist circumference increased, such that there was no association among subjects with low concentrations of OC pesticides, while waist circumference was strongly associated with HOMA-IR among subjects with high concentrations of OC pesticides. The consistency of the patterns is thought provoking, even though the formal tests for interaction were not significant; the pattern leads to our hypothesis that the toxicity of POPs related to the risk of both insulin resistance and diabetes may substantially increase as people get fatter. Additionally, they suggest (but do not prove) that obesity may not be a sufficient cause of type 2 diabetes.

Among limitations, the cross-sectional study design in the NHANES does not allow inferences regarding the temporality of events and the causality between POPs and insulin resistance. Second, misclassification bias is possible for subjects whose POPs would have been detectable with a higher sample volume. Such misclassification would be nondifferential if sample volume is unrelated to HOMA-IR. Third, HOMA-IR is a surrogate but is highly correlated with insulin resistance measured using the euglycemic-hyperinsulinemic clamp method (20). Finally, inferences should be made cautiously in light of the multiple comparisons made, even given the strong agreement between the present findings and those related to prevalent type 2 diabetes (1).

In summary, along with our previous finding on the association between POPs and diabetes, our current study raises particular suspicion that OC pesticides and nondioxin-like PCBs may be involved in the pathogenesis of insulin resistance, which may explain part of the excess risk for diabetes, associated with POPs more generally. Especially, the interaction between OC pesticides and obesity on the risk of insulin resistance and diabetes suggests that POPs stored in adipose tissue may play a role in the current epidemic of type 2 diabetes.

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